Factors associated with outcomes of patients placed on tuberculosis treatment in the western geographic service area of Cape Town

Minor-Dissertation by

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DECLARATION

I, Irene Nyoni (NYNIRE001), hereby declare that the work in this minor-dissertation is based on my original work (except where acknowledgements indicate otherwise) and has not, in whole or in part, been submitted towards another degree, at this University or elsewhere.

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Signed by candidate

Signature

November 2017

Date

University of Cape Town

DEDICATION

I dedicate this thesis to my God Jehovah, who gave me strength to do all things through Him and to my family especially my mother.

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I want to express my gratitude to the TDRC management for giving me time off work to pursue my MPH

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ABSTRACT

Background

In the Western Cape Province of South Africa, tuberculosis (TB) is a major health problem and in 2012 accounted for 7.40% of premature deaths. The Province has experienced an increase in TB incidence in the past 20 years.

Objectives

The aims of the study were to describe the distribution of tuberculosis and identify risk factors associated with TB treatment outcomes in public sector tuberculosis facilities in the Western Geographic Service Area of the Cape Town Metropole District.

Methods

A cross sectional study was conducted using data collected in electronic TB registers from June 2011 to July 2012. Patients initiated on TB treatment aged 15 years and above with a known treatment outcome were included in the study.

Results

The study included 10 251 TB patients registered during the study period who had a final treatment outcome and 55.35% (5 674) were males. The mean age was 36.0 years and 72.20% (7398) were new cases. Most patients had pulmonary TB (83.21%). Almost half of the patients (49.62%) were co-infected with HIV.

Of the 10 251 cases, 47.02% (4 820) completed treatment, 37.43% (3 837) were cured, 8.67% (889) defaulted, 5.18% (531) died and 1.70% (147) failed treatment. There was a significant association between treatment outcome and sex, disease classification, treatment regimen, HIV status and patient category.

Conclusion

A high proportion of incident TB cases had previously been treated for TB. Overall treatment outcomes were poor. Unfavourable treatment outcomes were more common in men, those with extra pulmonary TB, retreatment patients and those co-infected with HIV.

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PART A: PROTOCOL

Background

The World Health Organization (WHO) reported that the fight against tuberculosis (TB) has yielded some positive results in the reduction of cases and deaths.[1] Although progress has been noted in the targets set in the Millennium Development Goals such as a 2% decline in TB incidence rate and 45% decline in the mortality rate since 1990, TB remains a major global health problem.[1] It causes morbidity each year in millions of people and is the second leading cause of death from an infectious disease worldwide following Human Immunodeficiency Virus (HIV).

Global burden of Tuberculosis

According to the WHO Tuberculosis report 2013, in 2012 there were 8.6 million new cases of TB disease and 1.3 million TB deaths (including 320 000 deaths among HIV-positive persons). About 13% of the 8.6 million people with TB in 2012 were HIV positive and 75% of these cases were from Africa. Most TB cases including deaths occurred in men but the burden of disease among women was also high. There was an estimated 410 000 TB deaths among women in 2012 including 160 000 among HIV-positive women.[1] WHO recommends the global TB strategy in the treatment and control of TB and 56 million people were successfully treated for countries that had adopted WHO global TB strategy between 1995 and 2012 saving about 22 million lives.[1] The target set by World Health Assembly in 1999 for treatment success is 85% and the global cohort that was treated in 2011 (2.6 million) as new cases of sputum smear-positive pulmonary TB attained 87% treatment success, meeting and exceeding the excepted treatment success rate however, the African region had 82% which is slightly below the set target.[1]

TB control and Treatment

WHO recommends following the DOTS programme in the control of TB. The programme consists of five elements; political commitment, case detection by sputum microscopy, standardized short-course chemotherapy, sustainable drug supply and standardization of recording and reporting. Most national TB programmes have adapted this programme in the fight against the spread of TB and strive to reach treatment completion rates of 85% and case detection rates of 70% which are required to have an impact on the TB epidemic.[2] On the other

hand WHO developed TB Treatment guidelines and recommendations that TB control programmes in most countries have adopted. The aims of the tuberculosis treatment programme are; to cure patients of the infection and to restore their quality of life, to prevent death or prolonged ill health due to TB, to prevent the relapse of TB, to reduce transmission of TB to others as well as to prevent the development and transmission of drug resistance.[2]
The strength of TB control remains in establishing and managing standardized treatment across the country for all TB cases – sputum smear-positive, smear-negative, and extra pulmonary. It is advised that in all cases, WHO guidelines on patient categorization and management are followed.[2] South Africa is currently using the 2013 treatment guidelines.

TB Treatment outcomes

Monitoring treatment outcomes is one component that is essential for understanding the effectiveness of TB control programmes[3] and lead to the identification of risk factors for unsuccessful treatment and specific high risk groups that need targeted efforts.[4] The outcome categories follow the guidelines set by WHO and include the treatment outcomes; cured, treatment completed, treatment failure, died, defaulted or transferred out.[2] These treatment outcomes are defined as follows;

- Cured; a patient whose sputum or culture was positive at the beginning of the treatment but who has smear or culture that was negative in the last month of treatment and on at least one previous occasion.
- Treatment complete; a patient who completed treatment but who does not have a negative sputum smear or culture in the last month of treatment and on at least one previous occasion. The sputum examination may not have been done or the results may not be available.
- Treatment failure; a patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included are patients with multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or positive.
- Died; a patient who dies for any reason during the course of treatment.
- Default; a patient whose treatment was interrupted for 2 consecutive months or more.
- Transfer out; a patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown. Therefore, the final TB treatment can be categorized into successful outcomes and unsuccessful outcomes.

- Treatment success; the sum of cured and completed treatment.
- Treatment interruption: Those that interrupted treatment for two (2) consecutive days or more during intensive phase, two (2) weeks or more during continuation phase and those that interrupted treatment for two (2) months or more after the date of the last attendance from the last treatment (defaulters) were regarded as having interrupted treatment.[2]

The final TB outcomes are categorized into successful outcomes or favourable outcomes and unsuccessful outcomes or unfavourable outcomes. A successful outcome includes TB patients who are cured or have completed TB treatment; while unsuccessful outcome consists of defaulted, died or failed treatment.

One tool that allows the assessment of treatment outcome is the Electronic TB register (ETR.net). The register provides information on the socio-demographics of persons on TB treatment and their outcomes. It provides easy and convenient collection, compilation, and analysis of TB data on a continuous basis.[5] The advantages of the use of ETR.net include:

- Data entry is at district level.
- The reports are standardised allowing data to be compared at national level as well as at international level.
- It allows for cohort analysis matching case finding, smear conversion, treatment outcomes reports, HIV testing and services for TB patients.
- It has a patient listing which is a useful programme management tool to trace patient outcomes.
- The ETR.net has data check. This data entry validation offers flexibility to enrich analysis as TB/HIV care evolves.
- Reports and summaries are produced by any time period such as quarterly or yearly at all reporting levels.
- The register has security access passwords for administrators and workgroups.

The ETR.net has some pitfalls:

- No changes are allowed such as adding and deleting of reporting units or change of district boundaries.
- The ETR has a standard reporting generator that does not allow for easy interface with other software programmes as such a more advanced analysis requires other statistical packages.

- The register is district based and therefore, cannot focus on individual clinics. Clinic based performance review can be important in isolating areas to improve the TB programme performance.
- The system requires adequate human resource and if this is lacking, poor data quality and poor outcomes may be blamed on the system.

Tuberculosis in South Africa

South Africa has one of the worst tuberculosis epidemics in the world, with a high disease burden, incidence rates and HIV co-infection rates, and growing epidemics of multi-resistance and extensively drug resistance tuberculosis.[6] In 2012, 24% of new and relapse TB cases globally were from African countries and one quarter of these cases were from one country - South Africa.[1]The WHO reported that in 2012 South Africa was among five countries with the highest number of incident cases. These countries included India (2.0 million–2.4 million), China (0.9 million–1.1 million), South Africa (0.4 million–0.6 million), Indonesia (0.4 million–0.5 million) and Pakistan (0.3 million–0.5 million).[1] The estimated incidence of tuberculosis in South Africa in 2012 was 1003 cases per 100 000 population,[1] compared to 266 cases per 100 000 population in 2003.[7] Despite having the worst TB epidemic, South Africa has continued with efforts to prevent and control the spread of TB upholding the cornerstone of TB control of proper detection and treatment completion of new cases of TB disease under the DOTS programme. In 1995 the country adopted the DOTS programme as the standard care for TB although it has been noted that the implementation has not been consistent.[6] TB drug resistance surveillance has been enhanced and TB programmes and patients TB treatment outcomes are monitored through the TB register.[6] In 2012 in South Africa 296 996 new cases of TB were notified.[1] New cases are patients who have never previously had TB treatment or taken anti-TB drugs for less than 1 month.[2] They may have positive or negative bacteriology with the disease at any anatomical site. Of the new cases 40% (119 898) were smear positive, 21% (63 210) were smear negative and 24% (71 421) did not have a smear or the result was not known, while 14% (42 467) had extra pulmonary TB.[1] There were 52 586 retreatment cases (18% of all cases) where patients had previously received treatment for 1 month or more. Of the retreatment cases 51% were relapse cases (patients who were declared cured or treatment completed but reported back to the health service and were found to have a positive sputum smear), 6% were treatment after failure (patients who still had a positive bacteriological test after the completion of treatment), 15% were treatment after default (patients who had stopped

receiving treatment for more than 2 months) while 28% had another reason for retreatment.[1] Treatment success rate varied for the different treatment categories for the 2011 cohort included in the 2012 report, new smear positive and/or culture positive had a 79% treatment success rate, while new smear negative/extra-pulmonary had a 67% and retreatment cases had a 66% treatment success rate.[1] The achieved treatment success rates were below the WHO expected rate of 85%.

Tuberculosis in the Western Cape Province

In the Western Cape Province of South Africa, TB is a major health problem and in 2012 together with HIV and interpersonal violence, accounted for the largest proportion of premature mortality (HIV/AIDS; 12.0%, interpersonal violence; 9.2% and tuberculosis; 7.4%).[8] Historically, the Western Cape Province has had the highest rates of tuberculosis in the country.[9,10] It remains the province with the highest incidence of new TB cases and showed an annual increase of 8-10% in registered TB cases during the period 1997 to 2005.[11]

In the past 20 years the province has experienced an increased TB incidence rate particularly in the coloured population.[10] This population accounted for 42.4% of the Cape Town population in 2011.[12] Despite the increase in TB incidence there has however been a stable annual risk of infection in this high risk group.[8] The average annual risk of infection calculated as an average prevalence of infection, approximates the incidence of infection and indicates the extent of transmission in a community. This could reflect the high prevalence observed in the coloured community.[10] Claassens et al. attributed the increase in TB incidence to the inability of the health services to reduce new infections in the communities. Late presentation has also led to an increase in the infectious pool and this is aggravated by overcrowding and poor social conditions. There are also other risk factors for TB disease such as poor nutritional status, alcoholism and unemployment.[13] Poor patient compliance and several health service impediments have resulted in a large number of patients not being retained on treatment until cure.[10] The emergence of drug resistance TB also poses a threat to the control of the spread of TB. At the national level multi-drug resistant TB (MDR-TB) in 2013 comprised 1.8% of new cases and 6.9% of previously treated cases of TB in South Africa.[1]

In Western Cape, the cure rate for new smear positive TB is 80.5%, although below the WHO target of 85%, the rate is the highest TB cure rate achieved in South Africa.[14]

Cape Town Metro District

TB is a major contributor to the burden of disease in Cape Town with a 66% increase in the number of TB cases notified between 1997 and 2003.[15] Despite the reported increase in TB incidence in Cape Town the TB Control Programme aims to identify 80% of people who have TB and to cure them at the first attempt.[15]

TB caseload varies across the sub-districts of Cape Town and in 2002, half of the TB caseload came from the high burden sub-districts, Khayelitsha, Nyanga and Oostenberg. Athlone, South Peninsula and Tygerberg West sub-districts achieved cure rates of above 80%.[15] Site B clinic in Khayelitsha treated over double the number of TB patients than any other clinic in Cape Town and still managed to achieve a cure rate of 72% which is 2% higher than the district average.[15] High cure rates can be achieved in spite of huge caseload. In 2007 Khayelitsha was reported to have five high burden clinics accounting for 11% of the provincial burden.[11] Klipfontein, Eastern and Northern had three high burden clinics each while Mitchell's Plain and Western had two high burden clinics.[11]

The success of the TB control programme can be monitored by the assessment and review of treatment outcomes for patients that are initiated on TB treatment. Approximately 87% of persons with TB are managed by public sector services in Cape Town.[15]

TB/HIV co-infection

The HIV/AIDS epidemic has impacted on the incidence of TB.[16] It has been shown that HIV-positive individuals have about a 10% annual risk of TB disease or active TB and a more than 30% life time risk of developing TB disease.[11] In South Africa HIV prevalence in incident TB cases were estimated at 63% in 2012 or 330 000 of persons put on treatment for new TB were co-infected with HIV.[1] Co-infected patients have an increased risk of morbidity and mortality with TB being the leading cause of mortality among HIV infected patients in TB endemic countries, even in the presence of access to antiretroviral therapy (ART).[17] In 2012 in South Africa the mortality rate was 168/100 000 for co-infected persons while the mortality in uninfected persons was 59/100 000 showing that HIV is associated with increased mortality.[1] HIV infection increases the risk of reactivation of latent TB 20-fold with a much higher risk in patients who have clinically advanced HIV disease.[18] The HIV prevalence in Cape Town in

2012 was 5.2%, the lowest recorded among metropolitan municipalities.[19] The HIV status of 84% of TB patients was known and 65% of these patients were co-infected with HIV.[19]

Monitoring the distribution of TB in adults, the way in which TB was diagnosed, the presence of HIV co-infection as well as the outcomes is essential for understanding the effectiveness of TB control programmes[20] and identifying specific high risk groups that should be targeted.[21] Furthermore, the success of the TB control programme can be monitored by periodic assessment and review of treatment outcomes for patients that are initiated on TB treatment.

Research Question

To describe the distribution of tuberculosis in persons with treatment outcomes at public sector clinics and the risk factors associated with TB treatment outcomes in the Western Geographic Service Area (GSA) of the Cape Town Metropole District.

Purpose

The purpose of this study was to describe the characteristics of persons placed on TB treatment at public sector clinics and to describe factors associated with treatment outcomes so that appropriate interventions could be identified and implemented at these services.

Specific objectives

To describe the characteristics of TB patients placed on TB treatment at public sector facilities in the Western GSA of Cape Town according to the following variables:

- Demographics
- Patient category (new or retreatment)
- Disease classification pulmonary, extra pulmonary or both
- HIV status
- Tuberculosis Treatment outcome

To identify factors associated with TB treatment outcomes in the adult population placed on TB treatment at public sector facilities in the Western GSA of Cape Town.

Methods

Study design

This will be a secondary analysis using quantitative research methods and data collected in electronic TB registers (ETR.net) of adults placed on TB treatment at public sector facilities for the Western GSA Cape Town. This will be cross sectional study. ETR.net is an electronic TB register designed for TB/HIV surveillance used to monitor and evaluate the TB/HIV programmes. It is implemented at sub-district, district and provincial levels in all provinces of South Africa. It was implemented in all sub-districts in Cape Town in January 2003, with data backdated to July 2002. All patients initiated on TB treatment are monitored on ETR.net which captures patient-based information at the district level directly from paper TB registers and enables staff to monitor and evaluate TB programmes. At data entry level paper TB registers are checked for completeness and accuracy before entering data on ETR.net. The data is progressively entered throughout the treatment period and contains the following information; basic demographics, date of treatment initiation, treatment type (new or previously treated), bacteriological results, HIV status and treatment outcome.

Study setting

The Western Cape Department of Health and the Cape Town Health Directorate provide free TB treatment in primary health facilities in Cape Town. The Cape Town Metro is divided into eight sub-districts. The sub-districts are Southern, Mitchell's Plain, Klipfontein and Western (Western Geographic Service area) and Khayelitshya, Tygerberg, Eastern and Northern (Eastern Geographic Service area). We will use data from the Electronic TB register (ETR.net) collected from the Western GSA on patients who initiated treatment from June 2011 to July 2012.

Study population

The study population will comprise all TB patients aged 15 and above, inclusive of both new and retreatment cases in the TB registers and who have a treatment outcome. TB patients should have initiated treatment in the Western GSA of Cape Town Metropole between June 2011 and July 2012.

Inclusion and Exclusion criterion

Inclusion

- All TB patients 15 years of age and older
- With a final treatment outcome.
- Initiated on treatment between June 2011 and July 2012

Exclusion

- Patients aged less than 15 years will be excluded.
- Patients who were transferred out to other treatment centres or who were still on TB treatment at the end of the study period will be excluded because we cannot determine their treatment outcome.
- We will also exclude those who were transferred in because we will not have complete information on these patients.

Study size

The Cape Town Metro is divided into eight sub-districts. The sub-districts are Southern, Mitchell's Plain, Klipfontein and Western (Western Geographic Service area) and Khayelitshya, Tygerberg, Eastern and Northern (Eastern Geographic Service area). TB patients from the Western GSA, initiated on treatment from June 2011 to July 2012 with a treatment outcome will be included in this study.

Data management

Data from the ETR.net will be cleaned to ensure that only the needed data is analyzed. The cleaning will be done under the guidance of the supervisor ensuring that the date is double checked by the investigator and rechecked by the supervisor. The following variables will be analyzed;

- Age and sex
- Prevalence of TB for the study period stratified by sex and age stratified by sub-district
- Site of tuberculosis whether Pulmonary or Extra-Pulmonary TB
- Retreatment categories

    - Relapse (Pulmonary)
    - Retreatment after failure (Pulmonary)
    - Treatment after default
    - Other retreatment cases
- TB/HIV co infection
- Treatment outcomes

Statistical analysis

Statistical analysis will be done using the STATA version 12 for windows after importation of data from Microsoft excel. TB case notifications will be established for each sub-district and incidence rates will be calculated using data from the 2011 census. Baseline characteristics and treatment outcomes will be identified for the study population. Associations will be examined between characteristics such as age, sex and HIV status, patient treatment category and treatment outcomes using statistical tests such as chi-square test or fisher's exact test and measures of association. A P-Value of < 0.05 will be considered significant. All continuous variables will be described using means and standard deviations while categorical variables will be described using counts and proportions.

Strength and limitations of the Study

Strengths

The study is from a setting with a high burden of TB disease and the large number of patients in this database will provide accurate information on the factors associated with treatment outcomes.

Limitations

There may be missing or incomplete data that cannot be corrected since the study is using secondary data and we cannot go back to the original clinical records. The exclusion of those without treatment outcomes may give a biased evaluation as those excluded may have had poorer outcomes.

Ethical and legal consideration

Human Research Ethics Committee

The protocol will be submitted to the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town for approval. Data from the ETR.net will only be analyzed after ethical approval is granted. Permission to use the data was provided by the Research Section of the Health Department of the Western Cape and the database for the Western GSA was provided by the TB programme.

Privacy and Confidentiality

The database that will be used for the analysis will not contain any names nor addresses. Special identifiers will be used. Only aggregated information will be reported. Access to information and data of the study will be restricted to research members only.

Risk and benefits

There are no risks anticipated for TB patients by the use of data from ETR.net. Although there are no direct benefits to TB patients information gained from the study will help in the control of TB and the management of TB patients.

Resources

There is no budget requested for this study.

Logistics and time schedule

Time schedule

Gantt chart

	Feb 2015	March	April	May	June	July	August
Protocol writing							
Submission to ethics							
Data Analysis							
Dissertation write up							
Final submission							

Table 1: Variables

Variable	Variable type	
Registered TB patients	Discrete	Count
HIV status	Categorical	Positive or Negative
Treatment outcome	Categorical	C, TC, DF, F, D, TF, M
Sex	categorical, binominal	Male or Female
Patient category	Categorical	RC, RF, RD, OR
Patient treatment regimen	Categorical	1. New, 2. retreatment,
End of Treatment smear conversion results		New case (end of six months) Retreatment case (end of 8 months)

Reporting of results (including tables and figures)

Table 1: **TB proportions by age groups**

Age (years)	TB Proportions
15-24	
25-34	
35-44	
45-54	
55-64	
65-74	
>75	

Table 2- TB treatment outcomes

Dummy tables

Treatment outcome	Frequency	Percentage
Completed		
Cured		
Defaulted		
Died		
Failed		
Total		

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PART B: LITERATURE REVIEW

Tuberculosis

Background

Tuberculosis (TB) remains one of the most widespread infectious diseases worldwide and it has been exacerbated by the HIV pandemic. Although there is effective therapy for TB, it still poses a major health problem and it remains a major cause of morbidity and mortality in developing countries. According to the WHO, the recent intensive efforts to improve the collection and reporting of data on TB have shed new light on the epidemic, revealing that there are almost half a million more cases of the disease than previously estimated. The WHO's Global Tuberculosis Report 2014, shows that 9 million people developed TB in 2013, and 1.5 million died.[1]

The TB epidemic has been driven by the epidemic of HIV. Patients with both HIV and TB have increased risk of morbidity and mortality with TB being the leading cause of mortality among HIV infected patients in TB endemic countries in Africa, even in the presence of access to antiretroviral therapy (ART).[2]

According to the WHO, the life time risk of developing tuberculosis (TB) is estimated to be between 26 and 31 times greater in people living with HIV than among those without HIV infection. In 2013, there were 9 million new cases of TB, of which 1.1 million were among people living with HIV.

HIV infection increases the risk of reactivation of latent TB 20-fold[3] with a much higher risk in patients who have clinically advanced HIV disease.[4] There is also a high risk of recurrent disease especially in patients with a low CD4 cell count, with exogenous reinfection accounting for approximately two thirds of recurrent disease on the South African gold mines.[5]

South Africa is one of the African countries that has the highest burden of TB. The estimated incidence of tuberculosis disease was 1 003 cases per 100 000 population in South Africa in 2012.[6] TB is responsible for 5.4 % of total Disability-adjusted life years (DALYS) of the burden of disease in South Africa.[7] In 2012 in South Africa 296 996 new cases of TB were notified.[8] Of the new cases 40% (119 898) were sputum smear positive, 21% (63 210) were smear negative and 24% (71 421) did not have a smear or the result was not known, while 14% (42 467) had extra pulmonary TB.[6]

Western Cape Province

In the Western Cape Province of South Africa, TB is a major health problem and in 2012 together with HIV and interpersonal violence, accounted for the largest proportion of premature mortality (HIV/AIDS; 12.0%, interpersonal violence; 9.2% and tuberculosis; 7.4%).[9] Historically, the province has experienced an increased TB incidence rate particularly in the coloured population.[10] The coloured population accounted for 42.4% of the Cape Town population in 2011. .[11]

Despite the increase in TB incidence there has however been a stable annual risk of infection in this high risk group.[11] The average annual risk of infection calculated as an average prevalence of infection, approximates the incidence of infection and indicates the extent of transmission in a community.[12] This could reflect the high prevalence observed in the coloured community.[12] Claassens et al attributed the increase in TB incidence to the inability of the health services to reduce new infections in the communities.[11]

Yach reported that in the Western Cape late presentation for health care, led to an increase in the infectious pool and this was aggravated by overcrowding and poor social conditions. There were also other risk factors for TB disease such as poor nutritional status, alcoholism and unemployment. Poor patient compliance and several health service impediments resulted in a large number of patients not being held on treatment until cure.[13]

Although the province has a higher incidence than the national average it leads the country in its progress through the TB strategy. The cure rate for new smear positive TB is 80.5%, the highest TB cure rate achieved in South Africa.[14] The World Health Organization target is 85%.

Tuberculosis treatment

The tuberculosis treatment programme are aims to;

- Cure patients of the infection and to restore their quality of life.
- prevent death or prolonged ill health due to TB
- prevent the relapse of TB
- reduce transmission of TB to others
- prevent the development and transmission of drug resistance.[8]

The WHO developed TB Treatment Guidelines and recommendations that TB control programmes in most countries have adopted. The strength of TB control remains in establishing and managing standardized treatment across the country for all adult and paediatric TB cases. It is advised that in all cases, WHO guidelines on patient categorization and management are followed.[8] South Africa is currently using the 2013 treatment guidelines.

Diagnosis, treatment and outcome of TB patients are collected in the TB register. Information collected in the TB register can help improve the management of new patients. The outcome categories follow the guidelines set by WHO and include the treatment outcomes; cured, treatment completed, treatment failure, died, defaulted or transferred out.[8]

Monitoring the distribution of TB in adults, the way in which TB was diagnosed, the presence of HIV co-infection as well as the outcomes is essential for understanding the effectiveness of TB control programmes[15] and identifying specific high risk groups that should be targeted.[16]

Search Strategies

PubMed, MEDLINE, Scopus, MeSH database and journals in NCBI database were searched for studies on treatment outcomes for patients commenced on TB treatment. The key words included tuberculosis or TB and words related to treatment or therapy and outcome(s).

Key words: Tuberculosis, outcomes, risk factors, determinants, treatment

Study selection

This review included original reports which included primary and secondary studies. All reviews were excluded since the quality of the studies that are included in the reviews could not be accessed. Cross sectional studies that used TB registers as a source of data, as well as prospective cohort and retrospective studies that were either clinic- or hospital-based, were included.

Purpose

To perform a literature review on TB treatment outcomes and their determinants.

Review objectives

The purpose of this literature review was to identify risk factors associated with TB treatment outcomes in adults initiated on TB treatment. There are various factors that influence the possible treatment outcomes of patients initiated on TB treatment and these can be patient

related factors such as age and sex of the patient, the adherence pattern to prescribed treatment, alcohol use during treatment, education status as well as socio-economic status of the TB patients and whether coinfection with HIV is present. Other factors could be treatment related which include prior TB treatment and treatment services.

Summary of literature

Patient related factors

Age and sex

Age and sex have been found to be associated with TB outcomes in a number of studies. Fatiregun et al. in 2009 showed that sex was associated with poorer treatment outcomes in a cohort of sputum smear-positive pulmonary TB patients. This study was done at tuberculosis treatment centres in Ibadan, Nigeria and showed that being male was a significant risk factor for a poor treatment outcome compared to being female.[17] Similarly a study of 756 TB patients at a referral Hospital in northwest Ethiopia from 2010 to 2012 showed that death and defaulting was higher in females than in males and that older patients, rural residents and patients with EPTB were significantly less likely to have a successful outcome.[18]

Adherence to TB treatment

There were a number of studies on factors associated with adherence to medication. Adherence to treatment is defined as ingestion by patients of at least 90% of the expected dose. When patients are non-adherent, treatment is not taken according to the prescribed dosage or period resulting in poor treatment outcomes.

Studies reported many predictors for non-adherence to TB treatment. These include sex of the patient, age, poverty, severe psychological stress and alcohol use. Other predictors were availability of DOT and the different ways in which it is provided, the presence of co-infections and use of traditional medicines. Proper follow up of defaulters by health care worker TB trace teams was shown to encourage adherence.

Predictors of non-adherence to TB treatment which included being male, poverty, having more than one chronic condition, severe psychological stress and alcohol misuse were supported in a cross-sectional survey conducted in 2013 in 14 public sector primary health care clinics in

Northern Cape, Eastern Cape and KwaZulu-Natal of 3107 participants with new TB of whom 55.9% were co-infected with HIV.[19]

Directly Observed Therapy (DOT) has been advocated to ensure that patients adhere to treatment. Clinic approved observers witness the ingestion of TB treatment and this has had a great impact on reducing treatment default rates.[20, 21]

A study in 2012 in Tanzania from 93 health facilities in four districts (rural and urban) found that 95% of adult patients who opted for home-based treatment under the patient centred TB treatment (PCT) approach adhered to the treatment regimen. There was no decline in adherence when symptoms resolved in contrast to the conventional daily Health Facility-DOT approach where adherence declined.[22] The same study found that patients with treatment supporters more than 15 minutes walking distance away, were less likely to adhere to treatment than those staying in the same home.[22]

DOT is one component of the DOTS strategy to control TB. Where the DOTS strategy had been well implemented success rates exceeding 95% have been attained.[23] Case detection and cure rates are the main indicators of a well implemented DOTS programme, with global targets of 70% detection and 85% cure rate. Elzinga et al in 2004 reported that in high HIV prevalence populations such as those in Southern Africa TB incidence was increasing by 10% per year without the implementation of DOTS strategy. However a model predicted that attaining 70% detection and 85% cure rate would result in the trend being reversed from a 10% increase to a 4% decrease in TB incidence.[24] In order for the programme to work efficiently and effectively health providers must be fully engaged, [23] links must be built between public and private practitioners, health services must be available to all, [24] and global support provided to countries trying to reach their TB prevention, and treatment aims.[25]

Another study in 2007 in Bangkok investigated whether different ways of providing treatment support affected adherence including centre-based DOT, family-based DOT, self-administered treatment (SAT), centre-based DOT plus SAT and centre plus family-based DOT.[26] The centre-plus family-based DOT and family based DOT had significantly higher success rates when compared with centre-based DOT. Centre-based DOT plus SAT was almost five times more effective than centre-based DOT while SAT was the least successful.[26]

Lack of adherence to medication and treatment interruption were associated with death and relapse in a number of studies.[27, 28] In south-western Nigeria a retrospective review of the TB register from 2008 – 2011 showed that more treatment interrupters than those who adhere to

treatment died (54.1% versus 14.9%) and more relapsed (14.3% versus 3.4%).[27] Lack of adherence was shown to lead to TB Treatment failure in Burkina Faso, in a case control study conducted among pulmonary TB patients who began TB treatment in 2009 to determine risk factors for treatment failure.[29] Failure to take TB drugs for more than 14 consecutive days was a significant risk factor together with a positive sputum smear after two months of treatment, existence of comorbidity and use of traditional medicines or herbs.[29]

A historical cohort study of TB patients from 2004 until 2006 in Rio de Janeiro found that patients who self-administered treatment achieved a 72% cure rate.[30] Younger age and being alcoholic were significantly associated with treatment default.[30]

In 2004 a study in South Africa described adherence to standardized TB treatment and the effect of DOT on treatment outcomes. Patients who received partial DOT had an increased risk of an unfavourable outcome including death, treatment failure and default as well as patients who received DOT during either the intensive phase or the continuous phase.[31]

Bronner et al assessed the impact of the TB Tracer Project on treatment outcomes among TB patients with smear positive TB and registered in the Electronic TB Registry from 2007- 2009 in South Africa. Health care worker TB tracer teams traced TB patients who had interrupted treatment or had missed a clinic appointment to obtain a sputum sample which was used to assess the smear status for TB. The study used sub-districts as the unit of analysis, with each designated as either tracer (standard TB programme plus tracer project) or non-tracer (standard TB programme only). For all provinces combined, the percent quarterly change in proportion of TB treatment outcomes decreased significantly for default treatment outcomes among tracer sub-districts and increased significantly for successful treatment outcomes among tracer sub-districts. [32] A significant decrease in the proportion of patients defaulting was observed for all provinces combined over the time period comparing tracer and non-tracer sub-districts.[32]

Patient-related factors were also reported in a prospective cohort from 2005-2012 to be predictors of treatment outcome in South Korea.[33] Predictors of unfavourable outcomes at end of treatment (EOT) and end of study (EOS) in new or previously treated tuberculosis patients were identified. Both patient factors (diabetes status, age, BMI) and disease factors (history of multiple previous treatment episodes, MDR-TB) were significantly associated with treatment outcomes. Diabetes mellitus MDR-TB were significantly associated with poor treatment outcomes and relapse.[33] Those aged ≥50 years were more likely to have an unfavourable

outcome when compared to those aged 20-34 years. BMI ≥18.5 was negatively associated with cure .[33]

TB and HIV co-infection

Studies showed that HIV co-infection impacted on TB treatment outcomes. The optimal timing of ARV treatment of HIV infection was associated with better treatment outcomes. A study in Hong Kong from 1996 until 2009 showed that early ARV therapy in naive patients with tuberculosis was significantly associated with a more favourable outcome. However a higher proportion of patients initiated early experienced immune reconstitution inflammatory syndrome (22% vs 4%).[34] This was thought to be due to the low median CD4 counts of 74µl (range 29-181 µl) in those initiated early. However there were no deaths attributed to immune reconstitution inflammatory syndrome. On the other hand, Oshi et al. in 2014 determined predictors of successful treatment outcomes in co-infected TB patients in two health facilities in Ebonyi State, Southeast Nigeria, during 2011 and 2012. Overall, 65.8% of patients achieved successful outcomes.[35] The unsuccessful treatment outcomes were due to "default" (9.9%), "death" (19%), "treatment failure" (1.5%), and "transferring out" (3.8%).[35] Receiving care at a public facility and non-initiation of antiretroviral therapy were significant independent determinants for an unsuccessful outcome.[35]

Furthermore, only 53.4% of 219 co-infected patients had favourable outcomes, in a study in Malaysia in 2010 [36] and unfavourable outcomes were significantly associated with intravenous drug use, not receiving antiretroviral therapy, lymphadenopathy and low serum albumin .[36]

Service provision showed an impact on treatment outcome in co-infected patients in a study done from 2006 until 2009 in rural Mumbwa district, Zambia. TB treatment success rate improved significantly at sites that provided ART after the implementation of a mobile ART programme compared to non-ART sites.[37] Rates of HIV testing in TB patients also increased at ART sites[37]. Scaling up ART services in rural health facilities through a mobile ART programme greatly improved anti-tuberculosis treatment outcomes.

Alcohol use

Peltzer et al. in 2014 assessed factors associated with TB treatment failure, death and default in 40 public primary health care facilities in three districts (Siyanda in the Northern Cape,

Nelson Mandela Metro in the Eastern Cape, and eThekwini in KwaZulu-Natal). This prospective study showed that 70% of TB patients were either cured or had completed their TB treatment by the end of 6 months. Participants who lived in a shack or traditional housing, those previously treated for TB and those residing in the eThekwini district were significantly more likely to fail treatment, die or default.[38] Mukinda and others in 2012 also showed that the increase in rifampicin mono-resistant TB (RMR-TB) in the Cape Winelands-Overberg region was significantly associated with alcohol abuse .[39]

Finlay et al. in 2012 also showed that drinking any alcohol during TB treatment was significantly associated with defaulting treatment in South Africa.[40] The abuse of alcohol, being homeless and previous imprisonment were significantly associated with an unfavourable outcome in new pulmonary TB cases in Kazakhstan from 2000 to 2002.[41]

Socio-economic status and economic support

Studies showed that socio-economic factors affect TB treatment outcomes with the poor more likely to have an unfavourable outcome.[30] A cluster randomized controlled pragmatic trial in 2013 in a resource-limited setting in KwaZulu-Natal, South Africa tested the feasibility and effectiveness of delivering economic support to patients with pulmonary TB in a high-burden area. KwaZulu Natal had the second highest poverty rate in the country and more than half the population fell below the poverty line.[42] In the intervention clinic, TB patients were offered a monthly voucher of ZAR120.00 which was redeemed at local shops for foodstuff. Vouchers were provided until the completion of TB treatment. Patients in control clinics received the usual TB care. The economic support did not significantly improve treatment outcomes.[42] Finlay et al. found that TB patients who felt that food provisions could have helped them finish treatment, had a significantly higher risk of defaulting from TB treatment.[40]

Education

Early detection of TB depends on good health seeking behaviour and knowledge of the signs and symptoms of TB as well as the availability and accessibility of services. A study in 2014 in Rajshahi City, Bangladesh revealed that patients with pulmonary TB had greater knowledge about the symptoms, transmission, prevention and management of TB than those who had extra-pulmonary TB. Sex, age and educational status were also significantly associated with

level of knowledge. Female TB patients were significantly less likely and patients aged 21-35 years more likely to know about the transmission and prevention of TB.[43] Individuals with higher education and from urban areas were better informed about the symptoms and signs of TB disease.[43] A study in Nigeria by Fatiregun et al. also reported that poor knowledge of tuberculosis resulted in a higher risk of poor treatment outcomes compared to those with a good knowledge.[17]

Treatment related factors

Studies showed that a number of treatment-related factors were associated with TB outcomes. These include prior TB treatment and the integration of TB and HIV services.

Retreatment of TB

Retreatment may result from reactivation of persistent organisms after insufficient treatment of TB or from exogenous reinfection with TB.[44] A study in 2012 showed that episodes of retreatment TB between 2001 and 2010 in a high HIV and TB burden community of Cape Town were linked to first-episode treatment outcomes, HIV status and ART use. The study included 564 retreatment cases and showed that among HIV-negative patients, retreatment TB was predominantly due to reactivation following poor initial treatment outcomes while among HIV-positive patients re-infection TB was more common, particularly among those on ART.[44]

A study in Turkey in 2013 also showed that persons with an unfavourable TB outcome were significantly more likely to have had a previous history of TB. Patients with a history of interrupted treatment were 10 times more likely to default and patients with prior treatment failure were 17 times more likely to have treatment failure.[28] This was supported by Choi et al. in 2014 who identified previous treatment as a predictor of unfavourable outcomes and patients with more than 2 or more than 4 previous treatment episodes were significantly more likely to have an unfavourable outcome.[33]

Akpabio et al. identified treatment outcomes in hospitalised TB patients who were followed between from 2005 till 2007 in Ermelo in South Africa. More than two-thirds of the patients had completed TB treatment previously, and almost three-quarters (74%) of the patients had been treated within the previous 3 years.[45]

Integrated HIV/TB treatment services

Studies showed that linking TB and HIV treatment and prevention programmes improved the diagnosis, treatment and outcomes for patients who were co-infected with HIV.[46] Ikeda et al. showed co-infected patients at TB/HIV services in Guatemala were more likely to receive ART once services had been integrated (22% prior to versus 72% post integration) and they were significantly less likely to die.[46] Another study in Uganda showed that, integration of HIV and TB services resulted in improved TB outcomes and earlier ART initiation. More patients were started on ART during TB treatment (94% vs 78%) and mortality decreased in an integrated TB/HIV care centre when compared to the pre-integrated service.[47]

In 2013 Schulz et al. evaluated the outcomes of co-infected patients starting ART in a TB hospital in the Western Cape, South Africa. After the hospital stay, one group of patients received their treatment at an integrated TB and ART service while the other group received treatment from different providers. The vertical care model had significantly more unfavourable TB (28.7% vs. 5.9 %) and ART outcomes (30.1% vs. 7.4%) than the integrated care model.[48]

Ansa et al. assessed the impact of TB/HIV integration on TB treatment outcomes in Ghana. The study showed that TB/HIV integration significantly improved TB treatment success. In a before-and-after study in three hospitals the TB treatment success rate was 50% prior to, and 69% after integration.[49] Conversely in 2014 a study showed that there was no significant difference in treatment outcomes for newly registered, adult TB patients, including a subset of co-infected patients, at 13 integrated ART/TB primary healthcare facilities (PHC) compared to four single-service PHC facilities in 2009 and 2010. Integration was not associated with lower TB mortality and defaulter rates.[50]

In 2010 Howard et al. showed that successful integration of TB and HIV services in resource constrained settings was possible, although programmatic, infrastructure and staffing challenges still existed.[51] In Kenya a report on successes and challenges in an integrated TB/HIV clinic in a rural area with a resource limited setting also showed that the yearly odds of treatment success improved by 20% after the integration of TB/HIV services in resource-limiting settings.[52]

Reviews of routinely collected TB indicators

According to the WHO, treatment outcome is an important indicator for monitoring TB programmes. Maimela described the performance of the TB control programme in the Eastern Cape Province by evaluating treatment outcomes from 2003 to 2005.[53] A cure rate of 39.7% for new smear positive patients in 2005 was reported. The national target was 70% and this was reached by only one district. Successful treatment outcomes were below the 85% threshold suggested by the WHO.[53] Defaulting from treatment was a major challenge.[54] The study found that a lack of human resources was one of the major challenges.

Gafar et al. reviewed data from ETR.net from 2006 to 2010 in Limpopo Province by selecting a random sample of 1200 records.[54] New treatment cases, patients who received treatment at mine health facilities or those treated with regimen 3 had more successful treatment outcomes. Patients aged 22–55 years, patients with a history of defaulting and those who had received treatment at community health centre or village health facility were more likely to default on treatment. Patients that had failed treatment before, those that had received treatment at the hospital or mobile health facilities or were treated with regimen 2 experienced treatment failure more often. The testing rate for HIV amongst TB patients increased substantially from less than 1% in 2006 to 68% in 2010. This increased the number of known co-infected patients who initiated ART during the study period. Integrated HIV/TB services had also improved during the study period.[54]

Conclusion

TB continues to be a major contributor to morbidity and mortality globally and the HIV epidemic has had a major impact on TB prevalence. In the Western Cape, although the rate of co-infection is lower than the national average, TB rates are extremely high and a major contributor to the burden of disease.

The literature review identified patient-related and treatment-related factors associated with TB outcomes. Patient related factors such as age, sex, adherence to medication, co-infection with HIV and socio-economic status were identified as important risk factors for TB outcomes. Other factors were related to treatment and these were prior TB treatment and integration of TB and HIV services.

Treatment outcomes were associated with adherence patterns. Poor adherence is related to a number of factors. DOT has been recommended to ensure that TB patient take their drugs as prescribed. Studies showed that a combination of centre-based and family-based DOT yielded more successful treatment outcomes.

A number of interventions that improved outcomes have been identified. Integrated TB and HIV services have been shown, when well implemented, to improve treatment outcomes although more efforts are still needed to ensure adequate human and other resources.

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PART C- MANUSCRIPT

Manuscript is formatted according to the guidelines required for Bulletin of the WHO **submission guidelines.**

ABSTRACT

Background

In the Western Cape Province of South Africa, tuberculosis (TB) is a major health problem and in 2012 accounted for 7.40% of premature deaths. The Province has also experienced an increase in TB incidence in the past 20 years.

Objectives

The aims of the study were to describe the distribution of tuberculosis and identify risk factors associated with TB treatment outcomes in public sector tuberculosis facilities in the Western Geographic Service Area of the Cape Town Metropole District.

Methods

A cross sectional study was conducted using data collected in electronic TB registers from June 2011 to July 2012. Patients initiated on TB treatment aged 15 years and above with a known treatment outcome were included in the study.

Results

The study included 10 251TB patients registered during the study period who had a final treatment outcome and 55.35% (5 674) were males. The mean age was 36.0 years and 72.20% (7398) were new cases. Most patients had pulmonary TB (83.21%). Almost half of the patients (49.62%) were co-infected with HIV.

Of the 10 251 cases, 47.02% (4 820) completed treatment, 37.43% (3 837) were cured, 8.67% (889) defaulted, 5.18% (531) died and 1.70% (147) failed treatment. There was a significant association between treatment outcome and sex, disease classification, treatment regimen, HIV status and patient category.

Conclusion

A high proportion of incident TB cases had previously been treated for TB. Overall treatment outcomes were poor. Unfavourable treatment outcomes were more common in men, those with extra pulmonary TB, retreatment patients and those co-infected with HIV.

Background

Tuberculosis (TB) is still a major health problem internationally. It causes morbidity each year in millions of people and is the second leading cause of death from an infectious disease worldwide, following Human Immunodeficiency Virus (HIV). According to the World Health Organization (WHO) Tuberculosis report 2013, in 2012 there were 8.6 million new cases of TB disease and 1.3 million TB deaths.[1] Most TB cases including deaths due to TB occurred in men but the burden of disease among women was also high.

The World Health Organization (WHO) recommends the DOTS programme in the fight against the spread of TB. The programme consists of five components; political commitment, case detection by sputum microscopy, standardized short-course chemotherapy, sustainable drug supply and standardization of recording and reporting.[2] South Africa is among the countries in Africa that have the highest burden of TB[3] and has adopted the DOTS programme in its national TB programme and makes every effort to reach a 70% detection rate and 85% treatment completion rate required for an effective fight against the spread of TB.[2] In 2012 the WHO reported that South Africa had an estimated incidence of 1003 cases per 100 000 population.[1] In the same year, 296 996 new cases of TB were notified. Of the new cases 40% were smear positive, 21% were smear negative and 24% did not have a smear or the result was not known, while 14% had extra pulmonary TB.[1] There were 52 586 retreatment cases, who had previously received treatment for 1 month or more. Of the retreatment cases 51% were relapse cases, 6% were treatment after failure, 15% were treatment after default while 28% had another reason for retreatment.[1] In 2012 in South Africa, HIV positive incident TB cases were estimated at 631 per 100 000 population.[1]

In the Western Cape Province of South Africa, TB is a major health problem and in 2012 accounted for 7.4% of premature mortality.[4] TB is a major contributor to the burden of disease in Cape Town with a 66% increase in the number of TB cases notified between 1997 and 2003.[5] The HIV/AIDS epidemic has also impacted on the incidence of TB.[5]The HIV prevalence in Cape Town in 2012 was 5.2%, the lowest recorded among metropolitan municipalities.[6] The HIV status of 84% of TB patients was known and 65% of these patients were co-infected with HIV.

The Western Cape Department of Health and the Cape Town Health Directorate provide free TB treatment in primary health facilities in eight sub-districts in Cape Town. Despite the

reported increase in TB incidence in Cape Town the TB Control Programme aims to identify 80% of people who have TB and to cure them at the first attempt.[5] The success of the TB control programme can be monitored by the assessment and review of treatment outcomes for patients that are initiated on TB treatment.

Treatment follows the treatment guidelines recommended by the WHO[7], TB treatment is given for six to eight months depending on the regimen initiated. TB Treatment is provided in two phases. During the intensive phase four drugs in combination are given for five days a week, for two to three months. The second phase is the continuation phase, in which two drugs are given for five days a week, for four to five months. New TB patients are treated for six months, while retreatment patients are treated for eight months. Sputum tests are taken again after two months on treatment to check for progress, and at five or seven months to confirm whether the patient is cured.

The Western Cape Department of Health has adopted the WHO's DOTS strategy which includes directly observed therapy (DOT) to ensure patients adhere to treatment and this has been implemented in most clinics in the Western Cape. An important element of the strategy is the support and encouragement offered. TB clients are either observed taking their treatment at the clinic or at community level, by non-governmental organisations (NGOs) using volunteers as "treatment supporters" for the entire treatment period.[5] An integrated TB and HIV/AIDS strategy is also used where co-infected patients are treated for both TB and HIV and provided with Cotrimoxazole prophylaxis.[8]

Monitoring the distribution of TB in the adult population, the way in which TB is diagnosed, the presence of HIV co-infection as well as the treatment outcomes is essential for understanding the effectiveness of the TB control programme[9] and aid in identification of specific high risk groups that can be targeted in the fight against TB spread.[10] According to the WHO, treatment outcome is an important indicator for monitoring TB programmes.[2]

Cape Town has a high burden of TB, with cure rates ranging from 72% to 80%.[5] Continued monitoring of these cure rate will provide an assessment and review of treatment outcomes for patients that are initiated on TB treatment.

The Cape Town Metropole District is managed as two service areas. This study aimed to describe the distribution of TB at public sector TB facilities and to identify risk factors

associated with treatment outcomes in the Western GSA of Cape Town which consisted of 4 sub-districts namely, Klipfontein, Mitchell's Plain, Southern and Western.

Methods

A cross sectional study was conducted using data collected in electronic TB registers (ETR.net) for the Western GSA Cape Town from June 2011 to July 2012. ETR.net is used to monitor and evaluate the TB programme as it allows for cohort analysis matching case finding, smear conversion, treatment outcome reports as well as HIV testing and services for TB patients. The register provides easy and convenient collection, compilation, and analysis of TB data on a continuous basis. The register provides information on the demographics of persons on TB treatment and the outcomes. The categories of treatment outcome were cured (positive bacteriology at initiation and negative at completion), treatment completed (in the absence of bacteriological confirmation), treatment failed (positive bacteriology at the end of treatment), died and defaulted (treatment interrupted for more than 2 consecutive months).
A favourable treatment outcome included those who were cured or completed TB treatment, while an unfavourable outcome included those who defaulted, died or failed treatment. This is also known as the treatment success ratio. Factors investigated to determine if they are associated with outcome included sex, category of patient, type of TB and HIV status.

The protocol was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. All data were anonymised.

Statistical analysis was completed using the STATA version 14. Patient's characteristics were summarized using proportions. The Chi square test was used to examine the influence of variables on treatment outcomes.

Results

There were a total of 25 854 registered TB patients from the 4 sub-districts and 15 242 (59.0%) TB patients were over 14 years of age. Of the total registered TB patients 32.1% were from Mitchell's Plain, 26.9% from Klipfontein, 23.9% from Western and 17.1% were from Southern (Table 1).

The overall TB incidence rate (case detection rate) among the 4 sub-districts was 1041 cases per 100 000 population, with Klipfontein having the highest TB incidence rate (1 811 per 100

000 population) and Mitchell's Plain having the lowest TB incidence (745 per 100 000 population).

Only 67.3% (10 251/15 242) of patients above 14 years of age had treatment outcomes and of these patients with treatment outcomes, 32.8% patients were from Mitchells Plain, 26.8% from Klipfontein, 23.5% from Western while 16.9% were from Southern. Of the patients with treatment outcomes, 55.4% were males while 44.6% were females. Demographic and clinical data on these patients are shown in Table 2. The mean age was 36.0 years (SD12.42 and range 15 to 97 years). The mean age for females was 34.4 years while that of males was 37.4 years. Figure 1 shows the age distribution of the patients.

The majority of cases were new cases (72.2%) and 71.8% received treatment regime 1. Retreatment cases after relapse accounted for 8.3%, retreatment after default for 2.6% and retreatment after failure accounted for 0.6%. Other retreatment case with unknown or undocumented previous outcome were 16.4 % (Table 2).

The majority of the patients had pulmonary TB (83.2%) while 15.5% had extra-pulmonary TB and 1.3% had both types of TB (Table 2). There were more females with extra-pulmonary TB (51.9%) while more males had pulmonary TB (56.7%) as shown in Table 3.

HIV test results were available for 99% of the TB patients and almost half of the patients (49.1%) were co-infected with HIV. CD4 results were available for 96.5% of the HIV-infected patients and the mean CD4 count was 221 cells/mm^3 (range 0 to 1851). Of those who were HIV positive, 42.6% were on ART and 18.0% had been on ART before TB treatment was commenced.

Of all the patients placed on TB treatment 10 251 (67.3%) had a final treatment outcome, and of these, 47.0% completed treatment, 37.4% were cured, 8.7% defaulted, 5.2% died and 1.7% (147) failed treatment. Table 4 shows a detailed summary of treatment outcomes for registered TB patients during the study period.

Between June 2011 and July 2012 the treatment success rates of all registered TB patients with a final treatment outcome was 84.5%. The treatment success rate was 84.3% for patients with pulmonary TB, 85.8% for those with extra pulmonary TB and 80.8% for those with both pulmonary and extra pulmonary TB. New patients achieved a higher treatment success rate compared to those treated after failure (87.5% vs 66.1%, p=0.002) and subsequently patients placed on regimen 1 had a higher treatment success than patients on regimen 2 (87.5% vs

76.0%, p=0.000). Older TB patients (>65 years old) had a lower treatment success rate compared to those aged 25 to 35 years old (73.9% vs 84.5%, p=0.009) and co-infected patients also had a lower success rate compared to HIV negative TB patients (82.6% vs 86.6% p=0.000). There was no significant difference in success rate by sex (86.1% among females and 84.1% among males, P=0.692). Table 5 shows the variables associated with treatment outcome.

The study showed that specific treatment outcomes were associated with age, sex, patient category, disease classification, HIV status and treatment regimen as shown in Table 5. Age category 15 to 24 years experienced higher defaulter rates compared to those 45 to 54 years (10.0% vs 7.3%, P=0.000).

Although the sex of a patient was not associated with treatment success, more males had defaulted (9.8% vs 7.3%, P=0.000), nevertheless there was no difference between sexes in those that failed (1.8% vs 1.6%, P=0.742) and those that died (5.4% vs 4.9% P=0.315). Overall, there were more males compared to females among those with an unsuccessful treatment (60.2% vs 39.78% p=0.000).

More patients with extra-pulmonary TB died compared to those with pulmonary TB (6.9% vs 4.8%, P=0.000) and more patients with pulmonary TB defaulted from treatment (9.1% vs 5.9%, P=0.000).

More patients on regimen two than regimen one had unfavourable outcomes including default (14.4% vs 6.5%, p=0.000) and died (6.8% vs 4.6%, P=0.000) but there was no significant difference in those that failed (2.4% vs 1.4%, P=0.123). All the 8 (100%) TB patients on regimen 3 either completed treatment or were cured.

More retreatment than new TB patients had unfavourable outcomes with 14.5% defaulting compared to 6.4% (P=0.000), 6.7% dying compared to 4.6% (P=0.000), however there was no significant difference in those failing therapy, 2.4% compared to 1.4% (P=0.105). The defaulter rate was similar amongst HIV-positive and HIV negative patients (8.6% vs 8.6%, P=0.801) but a larger proportion of co-infected patients died (7.0% vs 3.3% P= 0.000).

Discussion

This study found a high incidence of TB in all four of the sub-districts that comprise the Western GSA of Cape Town. This is aggravated by the high prevalence of HIV.[5.11] More effort will be required to identify and cure all persons with TB to control this epidemic.

Most sub-districts in the Western Cape report a high caseload of TB patients.[5,11] The four sub-districts in this study had different caseloads with Mitchell's Plain contributed the largest number of patients compared to the other sub-districts, although it had the lowest incidence rate. Mitchell's Plain has been cited as one sub-district among others in the Western Province that has clinics with a high caseload and is characterised as a tuberculosis 'hotspot' geographical area. Theses TB 'hotspots' are areas with rapid urbanisation and high HIV prevalence.[11]

This study on the treatment outcomes of patients places on TB treatment in the Western GSA of the Cape Town District where there is both a high burden of HIV and TB, showed a high proportion of retreatment cases of TB (almost 28%) and poor treatment outcomes.

The proportion of retreatment cases is considered by many to be a measure of the quality of a TB control programme and poses a challenge to the control program. A study by Middelkoop et.al in 2012 also reported a high proportion of retreatment TB cases (28%) in Cape town.[12]

As in another study done in Cape Town,[13] our study showed that the rate of TB disease in a high prevalence area differs by age. Most TB cases were in the age group 25 to 44 years which are the productive years, indicating that TB may impact on the socio-economic conditions of the population. A study by Wood in 2010 in Cape Town showed that there were three peaks in TB incidence at 0-4 years, 20-24 years and 45-49 years of age. Our study which excluded children showed two distinct peak at 25 to 34 years and 35 to 44 years, [13] indicating an increased risk of infection with age and these are the age groups mostly affected with HIV infection.

Other studies have reported that males are at an increased risk of a poor treatment outcome compared to females.[14] In this study sex was associated with defaulting as in other reports and this may be attributed to the prevalence of high risk behaviours such as drug[15] and alcohol misuse[16] among men.

Naidoo et al showed that males were less likely to adhere to treatment compared to females [OR 1.26 (1.07-1.48) P<0.001] resulting in unfavourable treatment outcomes.[16] Sex and age of a patient were associated with treatment adherence in a Tanzanian study where female patients were two times more likely to adhere to treatment compared to male patients while patients 35 year to 44 years were more adherent to treatment compared to patients younger than 26 years of age.[17]

The majority of patients with TB (99%) were tested for HIV. In 2003 the Cape Town district adopted an integrated approach to TB and HIV/AIDS at primary health care level with all TB patients being offered HIV counselling and testing (HCT) and subsequent initiation of ART for co-infected persons at the same facility.[5] This allowed co-infected patients to access TB and HIV services at the same clinic and from the same health staff. Furthermore, 97% of co-infected patients had a CD4 count result recorded and 92% were on co-trimoxazole preventive therapy. These results were similar to those reported for Khayelitshya, Cape Town in 2010 where a decrease in the median time from the start of TB treatment to ART initiation was also observed.[18]

Although the HIV rate among TB patients in this study was lower than the national average (50% versus 63% in 2012), [1] only 43% of co-infected patients were on ART during the study period. Various studies have documented the benefit of ART in co-infected patients.[19] WHO guidelines recommend that all co-infected patients should be initiated on ART as soon as possible. The South African national TB treatment guidelines also require that all co infected patients be initiated on ART however, more than 50% of co-infected patients in this study were not on ART and the reasons for this should be explored.[20] It has being shown that co-infected patients not on ART were 5 times more likely have an unfavourable TB treatment outcome.[21]

The study showed that almost 9% of TB patients defaulted from treatment which is more than the WHO target of less than 5% and most defaulters were 15 to 24 years of age. Poor adherence to treatment results in patients remaining infectious longer and they are more likely to relapse or die. Targeted interventions to prevent defaulting in the younger age group are required. These could include the use of tracer teams and support to encourage compliance in this age group. Retreatment cases were also more likely to default, and particularly those who previously defaulted. Other studies have shown that patients with a history of interrupted treatment were 10 times more likely to default.[22]

The overall mortality among TB patients in this study was 5%. The proportion of co-infected persons who died was double that of HIV negative TB patients. HIV co-infection has been reported by other studies to be associated with higher mortality among TB patients[23] and that mortality has been shown to reduce when co-infected patients are cared for in a TB/HIV integrated service.[24] A higher proportion of patients with extra-pulmonary TB died compared to those with pulmonary TB. Extra-pulmonary TB was found to be an independent predictor for an unsuccessful treatment outcome in Nigeria.[25]

Limitations

There were missing data that could not be corrected since the study used secondary data and we could not go back to the original clinical record. The study only included patients with treatment outcomes, and it is possible that those excluded may have had poorer outcomes.

Conclusion

The study showed that the incidence of TB is extremely high in the Western GSA of Cape Town and that treatment outcomes are poor and that there is a high rate of retreatment. There is a need to reduce the number of co-infected patients not on ART by following the WHO recommendations to prioritise ART for co-infected patients. More deliberate efforts should be made to follow up TB patients who have previously had TB. We recommend enhanced supervision and monitoring, improved counselling and home visits, and early screening for TB in persons infected with HIV.

Figures and Tables

Table 1: Registered TB patients and TB incidence

Sub-District	# registered patients(All ages)	TB Patient above 14 years old	TB Patients with outcomes	Population*	TB incidence per 100 000 population
Klipfontein	6 957 (26.91)	4 063(26.66)	2 750(26.83)	384 189	1 811
Mitchells Plain	8 285 (32.05)	4 951(32.48)	3 364(32.82)	1 112 650	745
Southern	4 425 (17.12)	2 612(17.14)	1 727(16.85)	516 594	857
Western	6 187 (23.93)	3 616(23.72)	2 410(23.50)	470 541	1 315
Over all	**25 854 (100.00)**	**15 242 (100)**	**10 251(100)**	**2 483 974**	**1 041**

*Health District Profile – 2011

Figure 1: Age group distribution of TB patients

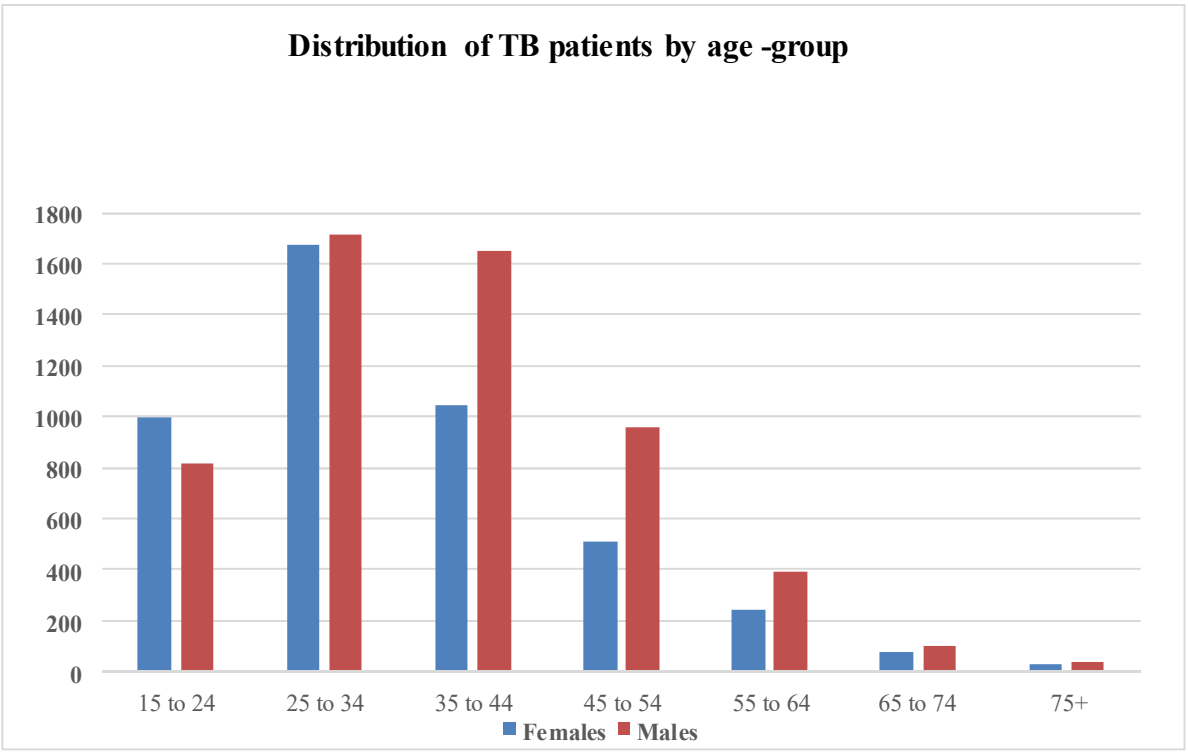

Table 2. Demographic and clinical profile of 10 251 TB patients

Variable		n (%)
Sex	Male	5 674 (55.35)
	Female	4 577 (44.65)
Age groups	15 to 24 years	1 809 (17.65)
	25 to 34 years	3 384 (33.01)
	35 to 44 years	2 701 (26.35)
	45 to 54 years	1 471 (14.35)
	55 to 64 years	632 (6.17)
	65 to 74 years	184 (1.79)
	Greater than 75 years	70 (0.68)
Sub-district	Klipfontein	2 750 (26.83)
	Mitchells Plain	3 364 (32.82)
	Southern	1 727 (16.85)
	Western	2 410 (23.50)
Treatment type	New	7 398 (72.17)
	Retreatment after Default	296 (2.62)
	Retreatment after Failure	59 (0.58)
	Retreatment after relapse	849 (8.28)
	Other Retreatment cases (unknown/undocumented previous outcomes)	1 676 (16.35)
Disease Classification		
	Extra-Pulmonary	1 591 (15.52)
	Pulmonary	8 530 (83.21)
	Both	130 (1.27)
Treatment Regimen*	1.2HRZE 4HR	7 357 (71.77)
	2.2HRZE 1HRZE 5HRE	2 886 (28.15)
	3.2HRZ 4HR	8 (0.08)
HIV status	Negative	5 016 (48.93)
	Positive	5 030 (49.07)
	Unknown	92 (0.90)
	Missing data	113 (1.10)
HIV-infected and on ART	Yes	2 145 (42.64)
	No	1 889 (37.56)
	Missing data	996 (19.80)
HIV-infected with CD4 count	With CD4 count	4 856 (96.54)
	No CD4 count	174 (3.46)
HIV-infected and on cotrimoxazole prophylaxis	Yes	4 636 (92.17)
	No	285 (5.66)
	Missing data	109 (2.17)

*HREZ stands for isoniazid, rifampicin, ethambutol, pyrazinamide given daily for the number of months indicated

Table 3-Disease Classification by sex

Sex	Disease Classification			Total
	Both	Extra-pulmonary	Pulmonary	
Female	59(45,38)	826(51,92)	3692(43,28)	4577(44,65)
Male	71(54,62)	765(48,08)	4838(56,72)	5674(55,35)
Total	130(100)	1591(100)	8530(100)	10251(100)

Table 4. Treatment outcomes of registered TB patients in Western GSA, Cape Town

Variables		Treatment outcome					Total
		Completed *n* (%)	Cured *n*(%)	Default *n* (%)	Died *n* (%)	Failed *n* (%)	
Treatment outcome		4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
Sub-district							
Klipfontein		1357 (49,35)	1010 (36,73)	202 (7,35)	146 (5,31)	35 (1,27)	2750 (26,83)
Mitchells Plain		1618 (48,10)	1229 (36,53)	283 (8,41)	171 (5,08)	63 (1,87)	3364 (32,82)
Southern		755 (43,72)	648 (37,52)	191 (11,06)	79 (4,57)	54 (3,13)	1727 (16,85)
Western		1090 (45,23)	950 (39,42)	213 (8,84)	135 (5,60)	22 (0,91)	2410 (23,51)
	Total	4820 (47,02)	3837 (37,43)	889 (8,67)	531 (5,18)	174 (1,70)	10251 (100)
Patient Category							
New		3577 (48,35)	2899 (39,19)	475 (6,42)	341 (4,61)	106 (1,43)	7398 (72,17)
After default		63 (23,42)	79 (29,37)	98 (36,43)	21 (7,81)	8 (2,97)	269 (2,62)
After failure		18 (30,51)	21 (35,59)	15 (25,42)	2 (3,39)	3 (5,08)	59 (0,58)
Relapse		331 (38,99)	329 (38,75)	120 (14,13)	50 (5,89)	19 (2,24)	849 (8,28)
Other		831 (49,58)	509 (30,37)	181 (10,80)	117 (6,98)	38 (2,27)	1676 (16,35)
	Total	4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
Disease classification							
Both		82(63,08)	23(17,69)	17(13,08)	8(6,15)	0(0,00)	130(1,27)
Extra pulmonary		1345(84,54)	20(1,26)	94(5,91)	110(6,91)	22(1,38)	1591(15,52)
Pulmonary		3393(39,78)	3794(44,48)	778(9,12)	413(4,84)	152(17,8)	8530(83,21)
	Total	4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
Age group category							
15 to 24		778(43,01)	793(43,84)	181(10,01)	33(1,82)	24(1,33)	1809(17,65)
25 to 34		1641(48,49)	1220(36,05)	334(9,87)	134(3,96)	55(1,63)	3384(33,01)
35 to 44		1322(48,94)	956(35,39)	229(8,48)	145(5,37)	49(1,81)	2701(26,35)
45 to 54		676(45,96)	550(37,39)	107(7,27)	108(7,34)	30(2,04)	1471(14,35)
55 to 64		286(45,25)	250(39,56)	23(3,64)	59(9,34)	14(2,22)	632(6,17)
65 to 74		86(46,74)	50(27,17)	12(6,52)	34(18,48)	2(1,09)	184(1,79)
75+		31(44,29)	18(25,71)	3(4,29)	18(25,71)	0(0,00)	70(0,68)
	Total	4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
Sex of patient							
Female		2339(51,10)	1604 (35,04)	335(7,32)	226(4,94))	73(1,59)	4577(44,65)
Male		2481(43,73)	2233(39,35)	554(9,76)	305(5,38)	101(1,78)	5674(55,35)
	Total	4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
HIV status							
Negative		1866(37,20)	2478(49,40)	432(8,61)	166(3,31)	74(1,48)	5016(48,93)
positive		2866(56,98)	1288(25,61)	430(8,55)	351(6,98)	95(1,89)	5030(49,07)
Unknown		38(41,30)	35(31,86)	12(13,04)	3(3,26)	4(4,35)	92(0,90)
Missing data		50(44,25)	36(31,86)	15(13,27)	11(9,73)	1(0,88)	113(1,10)
	Total	4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)
Treatment regimen							
2HRZE 4HR-Reg 1		3551(48,27)	2886(39,23)	478(6,50)	336(4,57)	106(1,44)	7357(71,77)
2HRZES 1HRZE 5HR-Reg 2		1262(43,73)	950(32,92)	411(14,24)	195(6,76)	68(2,36)	2886(28,15)
2HRZ 4HR Reg 3		7(87,50)	1(12,50)	0(0,00)	0(0,00)	0(0,00)	8(0,08)
Total		4820(47,02)	3837(37,43)	889(8,67)	531(5,18)	174(1,70)	10251(100)

Table 5. Variables associated with TB Treatment Success and unfavourable TB treatment outcomes

Treatment success rate n (%)		‡p value	Unfavourable Treatment outcome n (%)			§p value
Patient category				**Patient category**		
New	After failure			New	Retreatment	
6476 (87.54)	33 (66.10)	0.002	Default	475 (6.42)	414 (14.51)	0.000
			failed	106 (1.43)	86 (2.38)	0.105
			Died	341 (4.61)	190 (6.66)	0.000
Sex				**Sex**		
Male	Female			Male	Female	
4714 (83.08)	3943 (86.14)	0.692		960(60.23)	634(39.77)	0.000
			Default	554(9.76)	335(7.32)	0.000
			Failed	101(1.78)	73(1.59)	0.742
			Died	305(5.38)	226(4.94)	0.315
Age group				**Age group**		
25 to 34	65 to 75			15 to 24	45 to 54	
2861 (84.54)	136 (73.91)	0.009	Defaulted	181 (10.01)	107 (7.27)	0.000
Disease Classification				**Disease Classification**		
Pulmonary	Extra pulmonary			Pulmonary	Extra Pulmonary	
7187 (84.26)	1365 (85.80)	0.150	Died	413 (4.84)	110 (6.91)	0.000
Treatment Regimen				**Treatment Regimen**		
Regimen 1	Regimen 2			Regimen 1	Regimen 2	
6437 (87.50)	2212 (75.96)	0.000	Defaulted	478 (6.50)	411 (14.24)	0.000
			Failed	106 (1.44)	68 (2.36)	0.000
			Died	336 (4.57)	195 (6.76)	0.000
HIV status				**HIV status**		
HIV Negative	HIV Positive			HIV Negative	HIV Positive	
4344 (86.60)	4154 (82.59)	0.000	Defaulted	432 (8.61)	430 (8.55)	0.801
			Failed	74 (1.48)	95 (1.89)	0.483
			Died	166 (3.31)	351 (6.98)	0.000

‡p values indicate the differences in treatment success rate while §p indicates differences in unfavourable treatment outcomes within categories using the two sample test of proportions

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PART D- APPENDICES

Appendix A - Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shurette.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 December 2015

HREC REF: 924/2015

Prof D Coetzee
Public Health & Family Medicine
Falmouth Building
Entrance 5, level 4

Dear Prof Coetzee

PROJECT TITLE: FACTORS ASSOCIATED WITH OUTCOMES OF PATIENTS PLACED ON TUBERCULOSIS TREATMENT IN THE WESTERN GSA OF CAPE TOWN (Masters Candidate - Ms I Nyoni)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Ms Irene Nyoni will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

http://www.who.int/bulletin/contributors/current_guidelines.pdf

1. Scope and editorial policy

1.1 Content

The mission of the *Bulletin of the World Health Organization* is "to publish and disseminate scientifically rigorous public health information of international significance that enables policy-makers, researchers and practitioners to be more effective; it aims to improve health, particularly among disadvantaged populations".

The *Bulletin* welcomes a variety of unsolicited manuscripts (see below, 1.1.1.). These are initially screened in house for originality, relevance to an international public health audience and scientific rigour. If they pass the initial screening, they are sent to peer reviewers whose opinions are taken into account by the journal's editorial advisers when they decide whether to accept a manuscript for publication. Accepted papers are subject to editorial revision, which may involve substantive changes, shortening or restructuring the text and deleting superfluous tables and figures. The word limits given for each type of contribution do not include the abstract (where applicable), tables, boxes, figures and references or appendices, if any. The principal types of manuscripts are outlined below.

1.1.1. Unsolicited manuscripts

We welcome unsolicited submissions to the Research, Systematic reviews, Policy & practice, Lessons from the field and Perspectives sections of the *Bulletin*. All manuscripts destined for the first four of these sections must include two paragraphs indicating what they add to the literature. The paragraphs should briefly explain:

- what was already known about the topic concerned;
- what new knowledge the manuscript contributes.

Research

Research, methodologically rigorous, of relevance to international public health. Formal scientific presentations having not more than 3000 words and 50 references, plus a structured abstract (see below, 2.7); peer reviewed. As clear reporting is needed for readers and reviewers when judging the quality of research, studies should comply with the relevant reporting guidelines, available on the EQUATOR Network website, at: http://www.equator-network.org/about-us/uk-equator-centre/equator-publications/equator-network-publications-2010/. Operational and implementation research should be reported in compliance with the guidelines published in this issue (available at: http://www.who.int/bulletin/volumes/94/1/167585[1]). Intervention trials as defined by WHO (i.e. "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes") require registration in a public trials registry acceptable to the International Committee of Medical Journal Editors (ICMJE) before submission, and the registration number must be provided at the end of the abstract. Acceptable registries are listed at: http://www.who.int/ictrp/network/primary/en/. Web publication constitutes prior publication. This includes institutional websites that are open to the general public.

Systematic reviews

Exhaustive, critical assessments of published and unpublished studies on research questions concerning interventions, policies or practices in public health, with meta-analysis when feasible. Not more than 3000 words plus a structured abstract (see below, 2.7); the number of references in accordance with the scope of the review; peer reviewed. How studies were included and excluded should be illustrated in a flow diagram. Authors should strictly follow the reporting guidelines for systematic reviews and meta-analyses (PRISMA) available at: http://www.equator-network.org/reporting-guidelines/prisma/.

Policy & practice

Analytical assessments, debates or hypothesis-generating papers; not more than 3000 words and 50 references, plus a non-structured abstract (see below, 2.7); peer reviewed.

Lessons from the field

Papers that capture experiences and practice gained in solving specific public health problems in developing countries. Convincing evidence of effect should be provided. Not more than 1500 words and 15 references, plus a structured abstract (see below, 2.7); not more than one table and one figure; must include one box listing three lessons learnt; peer reviewed (see: http://www.who.int/bulletin/volumes/84/1/3.pdf). Operational and implementation research reports should follow the specifications described above for the research section.

Perspectives

Views, hypotheses or discussions (with a clear message) surrounding an issue of public health interest; up to 1500 words, no more than 12 references; peer reviewed.

1.1.2. Commissioned manuscripts

The categories of articles shown below are normally commissioned by the editors. Authors wishing to submit an unsolicited manuscript for one of these categories should first contact the editorial office (see below, 2.1).

Editorials

Authoritative reviews, analyses or views of an important topic related to a theme or to one or more papers published in a given issue; not more than 800 words, maximum 12 references.

Round tables

A base paper on a controversial current topic in public health (not more than 2000 words and an abstract) is the core of a debate by several discussants invited to contribute not more than 500 words each.

1.2 Ethical issues

The World Health Organization (WHO) publishes the results of research involving human subjects only if fully compliant with ethical principles, including the provisions of the World Medical Association Declaration of Helsinki (as amended by the 59th General Assembly, Seoul, the Republic of Korea, October 2008; available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and with the additional requirements, if any, of the country in which the research was carried out. Any manuscript describing the results of such research

must contain a clear statement to this effect and should specify that the free and informed consent of the subjects or their legal guardians was obtained and that the relevant institutional or national ethics review board approved the investigation. The *Bulletin* is a member of the Committee on Publication Ethics (COPE; see: http://publicationethics.org). Issues involving publication ethics may be referred to this committee by the editors. WHO Research Ethics Review Committee clearance is required for papers that report research supported by WHO or that are authored or co-authored by someone who was a WHO staff member while the research was conducted.

1.3 Competing interests

A competing interest arises when a professional judgement concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). We ask all authors to disclose at the time of submission any competing interests that they may have. Examples of competing interests may be found at: http://www.icmje.org. Further information on competing interests is available at: http://www.who.int/bulletin/volumes/83/9/645.pdf.

1.4 Funding

Authors should identify the sources that funded the work undertaken, affirm not having entered into an agreement with the funder that may have limited their ability to complete the research as planned, and indicate that they have had full control of all primary data.

1.5 Appeals process

Authors of rejected papers can appeal against the decision by following the procedures outlined in http://www.who.int/bulletin/volumes/83/9/645.pdf.

2. Preparation and submission of manuscripts

2.1 Correspondence

Manuscripts should be submitted to the *Bulletin* via our submissions website (http://submit.bwho.org), where full instructions are given. Queries about online submissions should be sent to: bulletin.submit.ask@who.int. Authors requiring assistance with online submission can contact the editorial office.

2.2 Uniform requirements

Manuscripts should be prepared in accordance with the *ICMJE recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals*. The complete document, updated in August 2013, is available at: http://www.icmje.org/recommendations/.

2.3 Languages

Manuscripts should be submitted in English and will be published in that language in the *Bulletin*; the abstracts are translated into Arabic, Chinese, French, Russian and Spanish.

2.4 Authorship

On the manuscript's title page authors should give their full names and the name, city and country of their institutions. The corresponding author must also provide a full postal address, which will be published with the email address unless otherwise requested. Academic titles and the names of departments and subdepartments are unnecessary and are discouraged for reasons of space. If an author has several affiliations, only the most important one should be provided. The criteria for authorship described in the *ICMJE recommendations* (see above, 2.2) must be rigorously observed. Each author should have participated sufficiently in the work being reported to take public responsibility for the paper's content and should describe in detail on the online submission system (not within the manuscript itself) his or her particular contribution. The *Bulletin* encourages submissions from authors in low- and middle-income countries, and in line with this policy at least one author should have a professional affiliation in the country where the study was conducted.

2.5 Licence for publication

The *Bulletin* is a fully open-access journal and charges no author fees. Authors are responsible for obtaining permission to reproduce in their articles any material enjoying copyright protection. They should send the letter granting such permission to the editorial office when they submit their papers.

On submission, the corresponding author must indicate agreement on behalf of all authors that their submission, if accepted, will be published under the intergovernmental organizations' creative commons attribution licence (CCBY 3.0 IGO).

2.6 Figures, tables and boxes

These should be used only to enhance the understanding of the text, not to repeat what can be clearly communicated within the text. All figures, tables and boxes should be numbered consecutively (e.g. Fig. 1, Table 1 and Box 1).

2.7 Abstracts

Abstracts should highlight the text's most important points and should be provided for the following types of papers: Research, Systematic reviews, Policy & practice, base papers for Round tables and Lessons from the field. The abstract should not exceed 250 words. It appears in English at the beginning of the paper and in Arabic, Chinese, French, Russian and Spanish between the end of the text and the reference list. Structured abstracts are required for Research papers and Systematic reviews (Objective, Methods, Findings, Conclusion) and for Lessons from the field papers (Problem, Approach, Local setting, Relevant changes, Lessons learnt).

2.8 Bibliographic references

Reference citations should be numbered consecutively as they occur in the text and references should be listed in accordance with the *ICMJE recommendations* (http://www.icmje.org/icmje-recommendations.pdf). The accuracy of all references is the authors' responsibility and authors are also responsible for dating access to URLs, providing a record of when they were active.

2.9 Maps

Papers should contain no maps unless an important finding cannot be conveyed without them or unless they are needed to make an essential point. Maps that show international borders, partially or in full, must be created from the following source, approved by the United Nations: http://www.un.org/Depts/Cartographic/english/htmain.htm following these standard operating procedures: http://gamapserver.who.int/gho/gis/training/DMF_GIS2010_2_SOPSforWHOMaps.pdf. A vectorial EPS (Encapsulated PostScript) file must be submitted. ■

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