Environmental health recommendations for Multidrug-Resistant Tuberculosis in low- and middle-income countries: a systematic review

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DECLARATION

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ABSTRACT

Despite efforts towards the management and prevention of Tuberculosis (TB) having shown some success, Multidrug-Resistant Tuberculosis (MDR-TB) may potentially compromise these endeavours. MDR-TB has the potential to become the most dominant form of TB in low- and middle-income countries (LMICs). The impact of environmental health factors on the optimization of health of MDR-TB infected individuals, as well as on the prevention of transmission to household contacts, is not well documented. Current Sustainable Development Goals (SDGs) aim to achieve inclusivity, sustainability and resilience, not only through economic and social changes, but also through environmental targets in order to achieve optimal health and well-being for all. However, without appropriate acknowledgment of the environment's influence on outcomes during TB treatment, these targets are potentially unattainable. Establishing the recommendations of environmental health risk factors for individuals living at home with MDR-TB will have important policy implications as well as assist in decision making for those affected with MDR-TB in LMICs, such as South Africa. This systematic review, therefore, sought to identify the environmental health factors in LMICs that affect treatment outcomes for individuals living at home with MDR-TB, to optimize their health during completion of their treatment regimen and prevent transmission to household contacts.

Part A outlines the current literature available for such a topic as well as methodology used within the systematic search and analysis of included articles. Prominent environmental health exposure variables of interest that have previously been identified as having a significant role in TB transmission or influencing the well-being of infected individuals, were identified within the literature. These included air pollution, nutrition, migration, urbanization, smoking, alcohol, other substance use and housing. Outcomes of interest included optimization of health and prevention of MDR-TB transmission to household contacts.

The article (part B) represents the results from the systematic search as well as the application to current policy recommendations. After screening and reviewing the full text of potential articles for inclusion (N = 87), only thirteen articles were eligible for inclusion into the final sample. All included studies were primary observational studies, examining the relationship between MDR-TB and the pre-defined exposures and outcomes in populations ≥13 years of age. Environmental risk factors for household transmission of MDR-TB potentially included malnutrition but

showed no significant relationship with overcrowding. There was disagreement as to whether smoking was as a significant predictor of mortality but findings did indicate that smoking did have a negative impact on sputum culture conversion among patients receiving treatment. Other substance use was found to have a significant role in the default of treatment. The use of alcohol was associated with poor treatment outcomes, default of treatment and lack of sputum culture conversion. In terms of household conditions, an association was found between substandard housing conditions and treatment default. Formal housing was associated with a decline in treatment default but a residential address change was associated with defaulting treatment. The results of the review presented contradictory results regarding the risk of mortality and underweight/overweight BMI estimates. The review potentially highlighted vulnerable population groups including gender groups, children and HIV positive individuals.

Therefore, this systematic review highlighted the potential relationship between environmental risk factors and optimising the health of individuals on treatment for MDR-TB, as well as the role that promoting environmental health may play in preventing the transmission to household contacts. In conclusion, environmental risk factors should be incorporated into local health system strategies and global policy. This includes WHO targets in TB prevention efforts, as well as in action areas for the attainment of relevant SDGs (e.g. SDG 3 and SDG 5), to address the burden of MDR-TB and decrease MDR-TB transmission in LMICs, effectively and sustainably.

Key words: multi drug-resistant, tuberculosis, environmental health, outcomes, transmission, systematic review

DEDICATION

To Benjamin, my son, may my efforts today make the world a better place for you someday.

ACKNOWLEDGEMENTS

Professor Hanna-Andrea Rother for her expertise, guidance and continual support. It was a great privilege to have her as a supervisor and mentor during this process.

Ms Mary E Miller for her knowledge and support throughout the entire process. I am so appreciative of her guidance, which enabled me to reach the final stage of this thesis.

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Abbreviations

BMI: Body Mass Index

CDC: Centers for Disease and Prevention

DRC: Departmental Research Committee

GNI: Gross National Income

HIV: Human immunodeficiency virus

JBI: Joanna Briggs Institute

LMICs: Low- and middle-income countries

MDR-TB: Multidrug-Resistant Tuberculosis

SDGs: Sustainable Development Goals

TB: Tuberculosis

UCT: University of Cape Town

UN: United Nations

WHO: World Health Organisation

XDR-TB: Extensively drug resistant TB

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1.1 INTRODUCTION

Tuberculosis (TB) is the second leading infectious disease, after COVID-19, which results in the most deaths globally.[1] Global estimates indicate that 9.9 million individuals acquired TB in 2020, with MDR-TB reported in 3.4% of new TB cases. This estimate increases by 18% in individuals who were treated previously for TB.[2] Despite efforts towards the management and prevention of TB having shown some success, Multidrug-Resistant Tuberculosis (MDR-TB) may potentially compromise these endeavours. MDR-TB has the potential to become the most dominant form of TB in low- and middle-income countries (LMICs).[3]

Particularly in South Africa, TB contributes to the quadruple burden of disease as a result of the existing significant presence of communicable and non-communicable diseases. Communicable diseases include HIV and TB, maternal and child mortality; non-communicable diseases include cardiovascular diseases, cancer and diabetes.[4] MDR-TB results when the organism Mycobacterium Tuberculosis shows resistance to two dominant drugs in TB treatment - Isoniazid and Rifampin. Should a patient with MDR-TB not undergo adequate treatment, the mycobacterium may develop further resistance to treatment, resulting in extensively drug resistant TB (XDR-TB). XDR-TB is characterised by Isoniazid and Rifampin resistance as well as resistance to additional agents in the class of fluoroquinolone medications and one or more of the second-line drugs, including Amikacin, Kanamycin, or Capreomycin.[5] Early initiation of appropriate treatment is facilitated by the GeneXpert MTB/RIF assay, a relatively new investigation technique that has transformed TB control as it allows fast confirmation of TB disease and resistance to any treatment agents. It is, therefore, a very useful tool in MDR-TB prevention.[5]

Treatment of MDR-TB costs 20 times more than standard TB treatment, resulting in a significant economic burden in LMICs.[5] It is therefore clear that MDR-TB deserves priority attention from local and global platforms to accomplish current Sustainable Development Goals (SDGs) and World Health Organisation (WHO) targets aimed at reducing the burden of TB. Currently, these targets include reducing the TB incidence rate by 90%, reducing deaths caused by TB by 95% and ending the TB epidemic by 2030 (SDG 3).[6,7] The SDGs aim to achieve inclusivity,

sustainability and resilience, not only through economic and social changes, but also through environmental targets to achieve optimal health and well-being for all.[8] However, without appropriate acknowledgment of the environment's influence on MDR-TB transmission, TB treatment outcomes and the health of infected individuals and their contacts, these targets are potentially unattainable.

MDR-TB treatment requires complex medication regimens which are long in duration and often cause serious side effects and secondary health risks, with poorer outcomes and higher deaths.[9,10] The vulnerability of LMICs to the growing incidence of MDR-TB is further exacerbated by inappropriate adherence to treatment regimens and poor surveillance in TB control programmes.[9,10] This poses a significant burden on fragile health care structures within LMICs. Even though primary infection with MDR-TB is more likely to occur than acquired resistance due to non-compliance with therapy, both of these circumstances highlight important implications for environmental controls for MDR-TB.[11] Current prevention and treatment efforts are targeted at: initiating appropriate treatment without delay, minimizing the progression of disease through the use of preventative therapy, reducing transmission, improving infection control mechanisms, incorporating drug susceptibility testing for fast TB diagnosis and contact tracing among vulnerable groups. The importance of addressing environmental health factors within these strategies is not well represented.[12] Evidence suggests that an outpatient care model can amplify treatment success and should be the focus of MDR-TB surveillance, treatment and control, with inpatient facilities such as hospitals only utilised to attain increased treatment outcomes and adherence rates.[13] Furthermore, treatment in a community setting is also growing in popularity, predominantly due to the lack of bed space and specialised facilities for MDR-TB treatment in LMICs.[14] Therefore, relying on institutional capacity to assist in reducing the growing prevalence of MDR-TB is unrealistic. This further accentuates the need for environmental health target priorities determined through local and national health stakeholder engagement and integrated within treatment programmes for MDR-TB. This is especially important if treatment is occurring in a community setting while infected individuals are living at home. Considering the above, the relationship between effective environmental health recommendations in the prevention of transmission to household contacts and the optimization of health for individuals living at home with MDR-TB, has important policy implications, especially in LMICs.

Although some meta-analyses have reported on the individual risk factors for MDR-TB in adults, the overall impact of environmental health risk factors on transmission to household contacts and optimization of health, specifically LMICs, is not well documented.[15,16] Optimization of health refers to "a deliberate, iterative and data-driven process to improve a health intervention and/or its implementation to meet stakeholder-defined public health impacts within resource constraints".[17] Previous studies have quantified optimization of health through health related quality of life measurements,[18,19] functional capacity measurements and cardiovascular endurance,[20] confirmation of new TB cases[21] and nutritional status, including Body Mass Index (BMI) estimates.[22]

1.2 The transmissibility of MDR-TB

A decelerated bacteriological response to MDR-TB treatment and failure of treatment, may increase the chance of transmission within a local community.[23,24] Furthermore, household contacts of individuals with MDR-TB possibly have a higher chance of acquiring TB as compared to individuals who are exposed to drug sensitive tuberculosis.[25] Importantly, infection and transmission of MDR-TB encompasses the same risk factors as drug-sensitive TB, and approaches toward transmission of standard TB are already well known regarding environmental factors that affect vulnerable and poorer groups.[26] Environmental factors at a population level that relate to MDR-TB transmission, include poor living conditions, alcohol use, poor nutrition, smoking, other substance abuse, and air pollution. Environmental health risk factors may be exacerbated by certain underlying social determinants which are important to consider in the transmission, treatment, and surveillance of MDR-TB.[27,28] These identified environmental health risk factors, within well described underlying social determinants, are the focus of this review.

1.3 Poverty, socioeconomic factors and MDR-TB

The highest TB burden occurs mostly within LMICs, as poverty contributes to the burden of TB and MDR-TB.[29] This causes significant challenges for MDR-TB treatment and surveillance programs, resulting in insufficient compliance, loss to follow-up and continued transmission.[29] This may also result from competing priorities that poorer populations face.[29] It is, therefore, imperative that social determinants and root causes of poverty are addressed when analysing

environmental health risk factors**.** Recognition of the social determinants that impact environmental determinants of TB and specifically MDR-TB, is essential to effectively advocate for health policy and plan for adequate health resources. This includes recognising the inattention to basic human rights that contribute to injustice and inequity which are associated with MDR-TB. Disadvantaged groups are more likely to suffer poor housing, overcrowded living conditions, poor ventilation, limited sanitation, poor access to water and unhealthy environmental exposures.[30] In LMICs, rapid urbanisation and increasing human migration due to economic or climate reasons, result in substandard living circumstances that are ideal for the spread of MDR-TB. Urban and peri-urban areas which surround cities or towns, are suggested to have a higher risk of MDR-TB transmission.[31] This emphasises the need for national policies implemented at a community level to reduce MDR-TB transmission present in vulnerable population groups within these regions. Levels of government that are involved in environmental control should adapt to trends in urbanisation and migration, to appropriately manage MDR-TB transmission in vulnerable communities. This should include treatment and adherence campaigns targeted to community interventions, including advocating for better housing standards and social support.[31] The socioeconomic environment, therefore, can immensely impact the health and wellbeing of vulnerable communities, and more so with those affected by MDR-TB.

1.4 Air pollution

Communities at the greatest risk for MDR-TB potentially are those living closely to outdoor air pollution sources such as traffic and industrial areas, due to the observed association between TB and outdoor air pollution.[32] Some literature suggests that ambient air pollution exposure may potentially be a risk factor for MDR-TB.[32] Additionally, indoor or household air pollution is also an identified significant risk factor for MDR-TB.[33,34] There is also a potential relationship between indoor air pollution emitted by cooking sources using biomass fuels and TB risk.[35] Although the increased risk of TB is substantiated by some evidence, the relationship between MDR-TB treatment outcomes in households exposed to indoor and outdoor air pollution is not clear.

1.5 Malnutrition and food insecurity

Nutrition has been shown to greatly influence MDR-TB treatment. However, an alarming number of individuals with MDR-TB, especially in LMICs, face food-insecurity.[36] Poor

nutrition is thought to increase TB infection risk and impacts the immune response, making infected individuals more vulnerable to poor outcomes.[37] A study evaluating malnutrition specifically among patients with MDR-TB found that underweight individuals, due to poor nutritional status at diagnosis, were more likely to have a severe presentation, have increased adverse effects from MDR-TB or from using treatment medications and have an increased mortality in comparison to MDR-TB patients who were of normal weight.[38] The role of nutrition in MDR-TB treatment and prevention strategies has great policy potential and could be a pathway to optimise the health in individuals on treatment for MDR-TB.

1.6 Alcohol and substance use

Although alcohol and substance use are not exclusively environmental health risk factors, they play a significant role in influencing treatment outcomes in populations vulnerable to environmental factors. Previous evidence suggests that alcohol abuse is a risk factor for MDR-TB and alcohol abusers are particularly vulnerable to incomplete treatment for MDR-TB.[39] Additionally, the use of substances such as marijuana or mandrax, are common examples associated with unfavourable outcomes and default from treatment.[40] Therefore, exploring environmental health factors in vulnerable populations should take into account the role of alcohol and other substance use, to gauge their overall influence in not only the risk of MDR-TB, but how recovery from the disease is impacted.

The above socioeconomic and environmental health determinants of MDR-TB (housing conditions, urbanisation, migration, nutrition, alcohol, other substance use, indoor and outdoor air pollution) are not only risk factors that may facilitate vulnerability to infection, but also impact the inequities faced by vulnerable populations who live in environments not conducive to health and whose ability to access health care is compromised. It is therefore essential that these vulnerable populations that face the greatest injustice relating to environmental risk factors and MDR-TB are identified and prioritised in policy. Although global health organizations such as the WHO and other UN agencies have described targets and specific SDGs in favor of eliminating TB, efforts to achieve this require focus on specific environmental health strategies that are clearly defined and addressed through policy.[41]

1.7 Rationale

A systematic review of effective environmental health recommendations in the prevention of transmission of MDR-TB to household contacts and the optimization of health for individuals living at home with MDR-TB, has not yet been conducted.[42]

Treatment programmes for MDR-TB in LMICs have been shown to be cost effective. However, scaling up such treatment programmes requires extensive resources for TB surveillance and prevention that address the role of environmental health factors and the underlying social determinants.[43] Current treatment and prevention strategies are mainly focused on efforts to distribute medications, with little consideration given to the impact of the environment on treatment outcomes.[14,15]

With this in mind, acknowledging that this health issue exists within the complex social, political and economic backgrounds of LMICs, recommendations of a systematic review should appropriately consider the complexities of the contextual environment when providing policy recommendations. Therefore, recommendations and adaptations to current policy require that local needs, social support systems, and health care delivery capabilities are suitable when recommending, implementing, or scaling up an intervention. Establishing the recommendations around environmental health risk factors for patients living at home with MDR-TB will have important policy implications as well as assist in decision making for those affected with MDR-TB in LMICs, such as South Africa. Due to the gap in available literature, this review seeks to identify the current environmental health recommendations to optimize the health of individuals living at home while infected with MDR-TB and prevent transmission to household contacts, in LMICs.

1.8 Review question

What are the current environmental health recommendations for individuals in LMICs that are living at home while infected with MDR-TB, to optimize health and prevent transmission to household contacts?

The research question will be addressed through a systematic review. Since the systematic review will include observational studies only, there will be no comparison groups in the development of the Population Exposure Comparison Outcome (PECO) statement.

Using the PECO method, we can summarise the above topic into the following to assist with the search strategy development:

Population:

- Individuals (≥13 years of age) with MDR-TB living at home in LMICs

Exposure(s):

- Environmental health risk factors: nutrition, air pollution (indoor and outdoor), socioeconomic factors including urbanization, migration, alcohol, other substance use and home condition (e.g. overcrowding, ventilation, poor sanitation etc.)

Outcome(s):

- To optimize the health of individuals with MDR-TB (see definition)
- To prevent the transmission of MDR-TB to household contacts

1.9 Aims of study

To identify the current environmental health recommendations for individuals living at home with MDR-TB in LMICs.

1.10 Primary objectives

To meet the study aim, the following objectives were identified:

1. To identify current environmental health recommendations available in published literature to optimize the health of individuals living at home during completion of their treatment regimen, while infected with MDR-TB.
2. To identify current environmental health recommendations to prevent transmission to household contacts by individuals infected with MDR-TB, living at home during completion of their treatment regimen.
3. To make recommendations based on the study findings for policies and standards relevant for individuals infected with MDR-TB, who are living at home within LMICs.

2. Methods

The protocol is presented according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. This systematic review will be registered on PROSPERO once relevant ethics approval has been received.

2.1 Define the team

The team will consist of one principal investigator (Mrs. A. Nel) and two secondary investigators (Ms M.E.Miller and Prof. HA Rother). The principal investigator is responsible for the search of articles and with the help of a second investigator (Ms M.E.Miller); articles will be reviewed for eligibility according to the search criteria. In the case where there is disagreement of whether an article should be included into the final sample or not, the third investigator (Prof. HA Rother) will be consulted to make the final decision.

2.2 Definitions

2.2.1 Multidrug-Resistant Tuberculosis

As defined by the Centers for Disease and Prevention (CDC), MDR-TB results when the organism Mycobacterium Tuberculosis shows resistance to two dominant drugs in TB treatment - Isoniazid and Rifampin. XDR-TB is characterised by Isoniazid and Rifampin resistance as well as resistance to additional agents in the class of fluoroquinolone medications and one or more of the second-line drugs, including Amikacin, Kanamycin or Capreomycin [5] Therefore, XDR-TB will be included in the definition of MDR-TB within the specified search strategy of the systematic review to ensure all appropriate articles are identified, unless otherwise stated.

2.2.2 Low- and middle-income countries

LMICs which are the focus of this review, have been pre-defined by the World Bank for the current fiscal year (2021) and include countries within a pre-specified Gross National Income (GNI) per capita range.[44] GNI is defined by the WHO as a “measure of the total domestic and foreign value added claimed by residents” in a specific time frame.[44] A list of the LMICs suitable for this review is available from the World Bank's website.[45]

2.2.3 Optimization of health as an outcome

Although the definition of optimization of health regarding MDR-TB is broad, for the purposes of this review, it includes quantification of the following indicators using standardized outcome measurements:

- Treatment outcomes:
  - cure
  - default of treatment (incomplete treatment)
  - death
- Health status:
  - Body mass index estimates (kg/m^2)
  - cardiovascular endurance through walking
  - positive/negative sputum cultures
  - any other relevant and appropriate standardised measure that has been identified in the literature
- Functional assessments of activities of daily living.

2.2.4 Transmission to household contacts

Assessment of household contacts and their TB status includes a positive GeneXpert MTB/RIF assay of direct household contacts of persons with diagnosed MDR-TB. Direct household contacts include any individual residing within the same residence as the index case for more than one day a week.[46] Household contacts may include children under the age of 13.

2.3 Eligibility criteria

2.3.1 Inclusion criteria

The following inclusion criteria will be used:

- Studies evaluating populations ≥ 13 years of age (except if examining household contacts)
- Studies conducted in LMICs
- Studies evaluating environmental health risk factors that optimise health and/or prevent transmission to household contacts

- All primary observational studies will be included namely cross-sectional, case-control and prospective and retrospective cohort epidemiological designs
- Studies which examined the relationship between pre-existing MDR-TB (including XDR-TB) and the pre-defined exposures only: environmental health risk factors including nutrition, air pollution (indoor and outdoor), socioeconomic factors including urbanization, migration, alcohol, other drug use and housing conditions (e.g. overcrowding, ventilation, poor sanitation etc.)
- Articles will be included from the year 2000 and up until and including the current year of the study (2021) to ensure that only current research is evaluated in the systematic review.
- Only articles that are published in English will be included as translation of articles is beyond the scope of this study.
- Only articles for which the full text version is available will be included as retrieving articles which are not full text is beyond the scope of this study

2.3.2 Exclusion criteria

The following exclusion criteria will be used:

- Studies evaluating drug resistant TB other than MDR-TB or XDR-TB
- Studies that evaluate the relationship between MDR-TB and other health conditions in a pre-specified population, such as HIV
- Studies that do not evaluate the environmental health recommendation categories relevant to the systematic review i.e. environmental health recommendations not specific to nutrition, air pollution (indoor and outdoor), socioeconomic factors (urbanization, migration, alcohol and other substance use and housing conditions)
- Studies using qualitative methods
- Studies which evaluated different outcomes other than that of optimisation of health and prevention of transmission of MDR-TB
- In the case of multiple publications with the same material or studies that have multiple publications in different journals, the most up to date version will be reviewed.
- Thesis or dissertations

- Narrative reviews, publications which do not use primary data and/or lack explicit method descriptions including expert opinion pieces

The PRISMA statement will be used to demonstrate the process of excluding and including literature for the final analysis.

2.4 Keyword selection

Since the above topic encompasses multiple factors, it is, therefore, imperative that this is reflected in the search terms to allow a thorough and systematic search of available literature. Table 1 describes the breakdown of main keywords used in the search strategy of this review.

2.5 Search strategy and study selection

The search for literature will be done through the following databases: Ebscohost (collections include Africa-wide information, Cinahl, Medline, health source nursing edition); Web of science (includes core collection and Scielo); Scopus and Pubmed. Gray (unpublished) literature will be reviewed by using Google scholar as well as searching reference lists of included articles, manually. A search strategy will be developed using the keywords listed above (Table 1) to ensure that all relevant and available literature will be incorporated into this review from the selected databases. An example of this search strategy has been presented in Table 2. The results from the electronic database search will then be reviewed for duplicates. The management of this process and further referencing management will be done in a citation manager, namely Endnote to ensure optimal management of references. The sample of articles after duplicates have been removed will then be screened via their title and abstract for eligibility for inclusion into the final sample. If it cannot be determined that the study meets the criteria based on the title or abstract, the full text will also be retrieved. If the inclusion criteria are met, the full article text will be retrieved. The final sample of eligible articles will then be assessed for final inclusion by reviewing the full text. Only articles for which the full text article is available will be included. This process will be conducted by two pre-identified reviewers. If there is uncertainty or disagreement regarding an article's eligibility for inclusion during the screening or full text review, then a third independent reviewer will be consulted for the final decision. After completion of identifying relevant articles, the third step will comprise a manual review of reference lists by the principal investigator to identify any other applicable articles and their

applicability for final inclusion will be decided. The flow of search results will be presented according to the PRISMA reporting standards described by Moher et al, 2009.[47]

Table 1: Breakdown of main keywords in search strategy

Main keyword	**Mycobacterium tuberculosis**	**Environmental Health**	**Transmission**	**Home condition**	**Malnutrition**	**Air Pollution**	**Socioeconomic factors**
Breakdown of alternative keywords	Tuberculosis	Risk factors	Household contacts	Overcrowding	Poor diet	Smoking	Substance abuse
	TB		Airborne transmission	Ventilation	Undernourishment	Proximity to industrial source of pollution	Migration
	Drug resistant			Poor sanitation	Starvation	Proximity to freeways	Urbanization
	Multidrug resistant TB				Under-nutrition	Use of firewood or paraffin for cooking or heating	Alcohol use
	Extensively drug resistant TB						

Table 2: Example of search strategy for environmental health recommendations to optimize health and prevent transmission to household contact of Multidrug resistant TB patients

Pubmed search string	(Tuberculosis, Multidrug-Resistant [MeSH] OR Extensively drug resistant TB [MeSH] OR Multidrug-Resistant Tuberculosis[Text Word] OR Multidrug-Resistant TB[Text Word] OR Drug-Resistant Tuberculosis[Text Word] OR Drug-Resistant TB[Text Word] OR MDR Tuberculosis[Text Word] OR MDR TB[Text Word] OR Extensively drug resistant Tuberculosis[Text Word] OR XDR TB[Text Word]) AND (Risk Factors [MeSH] OR Socioeconomic Factors [MeSH] OR Malnutrition [MeSH] OR Smoking [MeSH] OR Alcoholism [MeSH] OR Alcohol Drinking [MeSH] OR Population Dynamics [MeSH] OR Indoor air pollution [MeSH] OR Outdoor air pollution [MeSH] OR Overcrowding[Text Word] OR ventilation[Text Word] OR diet[Text Word] OR malnutrition[Text Word] OR malnourished[Text Word] OR undernourishment[Text Word] OR starvation[Text Word] OR smoking[Text Word] OR poverty[Text Word] OR socioeconomic[Text Word] OR alcohol[Text Word] OR alcoholism[Text Word] OR urbanization[Text Word] OR migration[Text Word]) AND (Infectious Disease Transmission [MeSH] OR Optimize health [MeSH] OR Transmission[Text Word] OR infectiousness[Text Word] OR containment[Text Word] OR prevention[Text Word] OR optimal health[Text Word])

2.6 Data extraction

The data from the final sample of included studies will be extracted and recorded in a data extraction form specifically designed for this review (Appendix 2). This process will be done by two pre-assigned independent reviewers. The final sample of included studies that met the inclusion criteria will have the following information extracted:

- primary outcomes
- study design
- country of origin
- author(s)
- year of publication
- journal
- study population
- sample size
- participant demographics (age, sex)
- recruitment process of participants

- exposure type
- outcome type
- association measure (RR/ OR/ PR)
- information of key indicators to further describe the studies' quality assessment.

Primary outcomes include optimization of patient health in MDR-TB and transmission prevention of MDR-TB to household contacts. The exposure variables of interest, categorically defined as air pollution, nutrition and socioeconomic factors will also be recorded. If it is found during the data extraction process that any data is not present, the study authors will be contacted to request the missing data. A table summarising the study characteristics of included studies will be provided.

2.7 Data synthesis and data analysis

Although it may be expected that there is a wide range of heterogeneity existing across the data, the reported relative measures of association with 95% confidence intervals will be extracted. Since observational study designs are included within the systematic review, the relative measures of association to be included will be relative risks (RR), hazard ratios (HR), prevalence ratios (PR) and odds ratios (OR). Both adjusted and unadjusted values will be extracted for incorporation into the data synthesis. In the event of available sufficient data, a meta-analysis will be conducted to summarise the outcomes of the included studies. A random effects model will be utilised to allow for any heterogeneity. The meta-analysis will be conducted using R. software.[48] Revman software will be used in this process to produce the forest plots.[49] If insufficient data is available or extensive heterogeneity exists then the results of the systematic review will be narratively described using tables and figures to present the results.

2.8 Heterogeneity

As stated, if a meta-analysis is possible, then the results of the meta-analysis will be presented by use of forest plots with corresponding summary statistics. Heterogeneity will therefore be assessed through visual inspection of these forest plots produced by the studies by comparing the position of the individual studies' confidence intervals in relation to the overall effect size. If intersection occurs through all confidence intervals, it will be concluded that heterogeneity is not present. Higgins (I) test will be used to provide a measure of variation (%) present in the studies

that results from heterogeneity instead of chance.[50] If large amounts of variation exist, possible sources of heterogeneity will be reviewed through subgroup analysis if appropriate given the available data. Potential sources of heterogeneity to be investigated include: study design, age groups, and diagnosis, treatment and follow up site (community facility versus specialised TB facility).

2.9 Quality appraisal

The authors will also assess the quality of the final sample of included articles using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort studies; the JBI Critical Appraisal Checklist for case-control studies; and the JBI Critical Appraisal Checklist for analytical cross-sectional studies.[51] The quality appraisal using the relevant tool will be managed in Review Manager Software. If the two pre-assigned reviewers note any disagreements, a third independent reviewer will be assigned to review the discrepancy. The results will be presented using visual graphs. A funnel plot will also be used, if possible given the available data, to evaluate any publication bias that may exist, by examining its symmetry.[52]

2.10 Ethical considerations

Ethical approval will be sought according to the University of Cape Town, School of Public Health and Family Medicine's Departmental Research Committee's (DRC) procedure for ethics approval for systematic reviews.

3. Declarations of interest

The authors declare that they do not have any conflicting interests.

4. Disclaimer

The opinions and views expressed in this review protocol are those of the authors and do not necessarily reflect the views of their affiliated institutions.

5. Timeline

	August 2020 - April 2021	4th May 2021	18th May 2021	June 2021	July 2021	August 2021	September 2021	October 2021	30 November 2021	15 December 2021	31 January 2022
Protocol write-up											
Ethics submission (DRC)											
Database search											
Screening of potential articles (abstract/title)											
Finalize final included sample											
Data extraction											
Data analysis											
Write up results and finalise article											
Submit letter of intent											
Turnitin Submission											
Submission deadline											

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PART B: JOURNAL READY MANUSCRIPT

Journal Name: South African Medical Journal (Annexure A)

Title: Environmental health recommendations for Multidrug-Resistant Tuberculosis in low- and middle-income countries: a systematic review

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Abstract

Background: Multidrug-Resistant Tuberculosis (MDR-TB) has the potential to become the most dominant form of Tuberculosis (TB) in low- and middle-income countries (LMICs). The impact of environmental health factors on the optimization of health in MDR-TB infected individuals, as well as on the prevention of transmission to household contacts, is not well documented. Current Sustainable Development Goals (SDGs) aim to achieve inclusivity, sustainability and resilience, not only through economic and social changes, but also through environmental targets in order to achieve optimal health and well-being for all. However, without appropriate acknowledgment of the environment's influence on outcomes during TB treatment, TB transmission and the well-being of infected individuals, these targets are potentially unattainable. Establishing the recommendations of environmental health risk factors for individuals living at home with MDR-TB will have important policy implications, as well as assist in decision-making for those affected with MDR-TB in LMICs, such as South Africa.

Objectives: To identify the environmental health risk factors in LMICs for individuals living at home with MDR-TB, to optimize their health during completion of their treatment regimen and prevent transmission to household contacts.

Methods: A systematic search of selected electronic databases was conducted during May 2021, including articles from 2000 up until 2021. Prominent environmental health exposure variables of interest that have previously been identified as having a significant role in TB transmission or influencing the well-being of infected individuals, were identified within the literature. These included air pollution, nutrition, migration, urbanization, smoking, alcohol, other substance use and housing. Outcomes of interest included optimization of health and prevention of MDR-TB transmission to household contacts. The systematic review was conducted according to PRISMA guidelines and underwent quality appraisal using Joanna Briggs Institute Critical Appraisal tools.

Results: After screening and reviewing the full text of potential articles for inclusion (N = 87), only 13 articles were eligible for inclusion into the final sample. All included studies were primary observational studies, examining the relationship between MDR-TB and the pre-defined exposures and outcomes in populations ≥13 years of age. Environmental risk factors for household transmission of MDR-TB potentially included malnutrition but showed no significant relationship with overcrowding. There was disagreement as to whether smoking was as a significant predictor of mortality but findings indicated that smoking did have a negative impact on sputum culture conversion among patients receiving treatment. Other substance use was found to have a significant role in the default of treatment. The use of alcohol was associated with poor treatment outcomes, default of treatment and lack of sputum culture conversion. In terms of household conditions, an association was found between substandard housing conditions and treatment default. Formal housing was associated with a decline in treatment default but a residential address change was associated with defaulting treatment. The results of the review presented contradictory results regarding the risk of mortality and underweight/overweight BMI estimates.

Conclusion: This systematic review, therefore, highlighted an important potential relationship between environmental risk factors and optimising the health of individuals infected with MDR-TB, as well as the role that promoting environmental health may play in preventing the transmission to household contacts. Environmental risk factors should be incorporated into local health system strategies and global policy. This includes WHO targets in TB prevention efforts, as well as in action areas for the attainment of relevant SDGs (e.g. SDG 3 and SDG 5), to address the MDR-TB burden and decrease MDR-TB transmission in LMICs, effectively and sustainably

Key words: multi drug-resistant, tuberculosis, environmental health, outcomes, transmission, systematic review

After COVID-19, Tuberculosis is currently the second leading infectious disease which results in the most deaths globally.[1] Despite some success in the management and prevention of Tuberculosis (TB), Multidrug-Resistant Tuberculosis (MDR-TB) may potentially compromise these endeavours. MDR-TB has the potential to become the most dominant form of TB in low- and middle-income countries (LMICs).[2] Particularly in South Africa, TB contributes to the quadruple burden of disease as a result of the existing significant presence of communicable and non-communicable diseases. Communicable diseases include HIV and TB, maternal and child mortality; non-communicable diseases include cardiovascular diseases, cancer and diabetes.[3] MDR-TB results when the organism Mycobacterium Tuberculosis shows resistance to two dominant drugs in TB treatment - Isoniazid and Rifampin. Should a patient with MDR-TB not undergo adequate treatment, the mycobacterium may develop further resistance to treatment, resulting in extensively drug resistant TB (XDR-TB). XDR-TB is characterised by Isoniazid and Rifampin resistance, as well as resistance to additional agents in the class of fluoroquinolone medications and one or more of the second-line drugs, including Amikacin, Kanamycin, or Capreomycin.[4,5] The current focus on the treatment and prevention of MDR-TB is mostly through new treatment regimens and treatment agents. However, a multi-pronged approach is

desperately lacking within current MDR-TB treatment ideals, including the under representation of the environmental influence on MDR-TB. Previous studies have reported on identified risk factors for MDR-TB in adult populations (e.g. diabetes mellitus and HIV).[6,7] However, the overall impact of environmental health risk factors on the optimization of health of MDR-TB infected individuals, as well as the prevention of transmission to household contacts, specifically in LMICs, is not well documented.

The vulnerability of LMIC populations to the growing prevalence of MDR-TB is exacerbated by inappropriate understanding of and adherence to treatment regimens, in addition to poor surveillance in TB control programmes.[8,9] This poses a significant burden on fragile healthcare systems within LMICs. Even though MDR-TB is more likely to emanate from a primary infection, instead of acquired resistance from poor compliance, both circumstances highlight the important implications of environmental controls for MDR-TB.[10] These also present important implications for vulnerable populations previously described as at risk for MDR-TB.[11-13] Treatment programmes for MDR-TB in LMICs have been shown to be cost-effective, however scaling up such treatment programmes requires extensive resources for TB surveillance and prevention that addresses the role of environmental health factors and the underlying social determinants.[14] Therefore, the relationship between environmental health recommendations in the prevention of transmission to household contacts and the optimization of health for individuals living at home with MDR-TB, has important policy implications, especially in LMICs. This involves incorporating environmental health in current efforts towards achieving Sustainable Development Goals (SDGs) and WHO targets. Currently, these include achieving a 90% reduction in TB incidence rate, 95% reduction in deaths due to TB by 2035, as well as ending the TB epidemic by 2030 (SDG 3).[15,16]

Current prevention and treatment efforts are targeted at: reducing transmission, improving infection control mechanisms, incorporating drug susceptibility testing for fast TB diagnosis, prompt initiation of appropriate treatment, contact tracing among vulnerable groups, and decreasing disease progression through preventative therapy. The importance of addressing environmental health factors within these strategies is not well represented.[17] A systematic review of effective environmental health recommendations in the prevention of transmission of MDR-TB to household contacts, and the optimization of health for individuals living at home with MDR-TB while on treatment has not been well explored in previous research.[6,18] Establishing guidance for environmental health risk factors for patients living at home with MDR-TB, in order to identify and develop targeted policy recommendations, will assist in decision making for LMICs tackling growing rates of MDR-TB.

Due to the gap in the literature, the review question identified the current environmental health recommendations for individuals in LMICs that are living at home while infected with MDR-TB, to optimize their health and prevent transmission to household contacts. The aim of the study was to identify current environmental health recommendations available in published literature and to make further recommendations based on the study findings for policies and preventative efforts.

Objectives

The following objectives were established, namely, to identify current environmental health recommendations to optimize the health of individuals infected with MDR-TB, while living at home during the completion of their treatment regimen, and to prevent transmission to household contacts by individuals infected with MDR-TB. The final objective was to make recommendations based on the study findings for policies and standards relevant for individuals infected with MDR-TB, who are living at home within LMICs.

Methods

Outcome definitions

Optimization of health

Although the definition of optimization of health regarding MDR-TB is broad, for the purposes of this review, it included quantification of the following indicators using standardized outcome measurements:

Treatment outcomes (cure, defaulted (incomplete) treatment, death), health status (Body Mass Index estimates (kg/m^2), cardiovascular endurance through walking, functional assessments of activities of daily living, positive/negative sputum cultures; or other relevant and appropriate standardised measures identified in the literature.

Transmission to household contacts

Assessment of household contacts and their TB status included a positive GeneXpert MTB/RIF assay of direct household contacts of persons with diagnosed MDR-TB. Direct household contacts include any individual residing within the same residence as the index case for more than one day a week.[19] Household contacts may include children under the age of 13.

Eligibility criteria

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The protocol of this review was submitted and published on the PROSPERO register (Protocol registration number: CRD42021255946). All primary observational studies evaluating populations ≥13 years of age in LMICs were included if they examined the relationship between MDR-TB and the pre-defined exposures and outcomes. Populations from adolescents (≥13 years of age) were included due to the varying definition of appropriate adult ages within the literature. Studies done on children (<13 years) were excluded, except if evaluating child household contacts of MDR-TB cases. Screening was conducted by one independent researcher (AN) and reviewed by a second independent researcher (MEM). Articles were included from 2000 up until and including the year of the study (2021), to ensure that only recent and current research was included. Only articles for which the full text version was available were included. Studies were excluded if they evaluated drug-resistant TB other than MDR-TB/XDR-TB, evaluated the environmental health recommendation categories not relevant to the systematic review, or used qualitative methods. To ensure that the findings and recommendations of this review remained generalisable to the general population, studies were excluded if they only included populations with another specific pre-existing disease. Duplicate publications of identical material, narrative reviews, and any

other publications which absent primary data, and/or a clear method description were also excluded.

Literature search

A systematic search of electronic databases was conducted during May 2021 using a predefined search strategy. This study received approval from the University of Cape Town, School of Public Health and Family Medicine's Departmental Research Committee. Databases that were searched included: Ebscohost (collections included Africa-wide information, Cinahl, Medline, health source nursing edition); Web of science (included core collection and Scielo); Scopus and Pubmed. After the removal of duplicates, the articles were screened via their title and abstract for eligibility for inclusion into the final sample. If the inclusion criteria were met, the full text of the article was retrieved. A review of the final sample of possible eligible articles for inclusion was done by evaluating the full text. Only articles for which the full text article was available in English were included in the final sample. After the completion of identifying relevant articles, a manual review of reference lists as well as a review of grey literature was done to identify if any other applicable articles met the inclusion criteria.

Description of study selection

The study selection results are presented in the PRISMA flow diagram (Fig. 1). After the initial screening of databases, a total of 1999 articles were found with an additional 14 articles included from manual searching of additional sources as described in the protocol (i.e. screening of reference lists, grey literature search and Google scholar). Initial screening of 768 articles without duplicates was conducted, of which 681 were excluded. Of the remaining 87 sample articles for full text review, 74 articles were excluded and 13 met the inclusion criteria for the final sample. The final sample, therefore, consisted of 13 articles which were included in the narrative synthesis.

Data collection process

The final included sample was then reviewed for data extraction. The data extraction process was done by one reviewer (AN) and final extracted data was reviewed by two independent researchers (MEM and AR). Articles that were included in the initial selection for full text review, but were identified as ineligible for the study, have been listed with reasons for exclusion within the PRISMA flow diagram (Fig. 1).

Quality assessment

Quality assessment of the final included sample was assessed using pre-specified standardized tools namely the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort studies, the JBI Critical Appraisal Checklist for case-control studies and the JBI Critical Appraisal Checklist for analytical cross-sectional studies.[21] This process was conducted by one independent reviewer (AN) and the final assessment was reviewed by two additional independent reviewers (MEM and AR).

Most of the included studies were cohort studies (n=11). All cohort studies met ≥7 criteria on the JBI checklist, with only one study meeting all criteria (11/11 score). The areas of most concern for cohort studies were the identification of confounders and strategies to deal with confounders of which only 3 articles reported doing this. Other under-performing criteria were follow up

completion, reasons for loss to follow up, and strategies to accommodate any missing data. One cross sectional study was included in the review, which met most of the quality assessment criteria (6/8). Potential confounders and strategies used to address these confounders were unclear within this article. Finally, one case control study was included in the review. This study met 8 out of 10 criteria for the quality assessment, although again, it was not clear if potential confounders were identified or if strategies were utilised to address confounders.

Results

Description of included studies

The extracted key study characteristics and main findings of the included articles have been presented in Table 1. The final sample included eleven cohort designs, one cross sectional study and one case control study. The variability in methodology contributed to the heterogeneity of the data, precluding any attempts at a meta-analysis. The final sample was grouped according to the two outcomes this review sought to analyze. Ten studies evaluated optimization of health outcomes and three evaluated disease transmission to household contacts as an outcome. Specifically, most studies assessing optimization of health, evaluated treatment outcomes and mortality in MDR-TB patients. The final sample evaluated various environmental health exposures including: smoking,[22-24] nutrition,[19,22 -28] household condition,[19, 27,29,33] alcohol and/or other substance use, [23,26,27,30-32] and migration.[31] The search yielded no eligible articles related to indoor/outdoor air pollution or urbanisation. The final sample of included studies was from various LMICs globally and evaluated MDR-TB and XDR-TB according to predefined definitions, which were appropriate for inclusion into the review sample. Additionally, all studies were undertaken in regions which have a significant TB burden according to the WHO. [34]

Transmission to household contacts

Studies examining transmission to household contacts found a non-significant relationship between child household contacts of individuals with MDR-TB who had confirmed TB disease and being underweight for their age (using BMI as an estimate). The relationship between exposure to household tobacco smoke and confirmed TB disease in child household contacts of individuals with MDR-TB was also not significant.[19] Additionally, overcrowding was not a significant predictor of TB disease among contacts of household members with MDR-TB.[29] Only one study evaluated nutrition, concluding that malnutrition in household contacts of MDR-TB positive household members, posed an increased risk of TB disease.[25]

Optimisation of health

Most articles evaluated outcomes relating to optimisation of health through mortality related outcomes, default of treatment and/or completion of treatment outcomes.[22,23,27,30,31] Two studies utilised sputum conversion as an outcome measure.[24,26] Smoking was identified as a significant predictor of mortality in one study,[22] however produced a contradictory result in another study.[23] Smoking was also found to have a significant adverse effect on sputum culture conversion in MDR-TB patients receiving treatment.[24,26] Substance use (marijuana or mandrax or unspecified) was identified as a significant risk factor for defaulting on treatment.[27,31,32] The use of alcohol was commonly reported as an indicator for poor treatment outcomes[30] and defaulting on treatment.[32] The use of alcohol was also found to be a significant factor negatively

affecting sputum culture conversion within individuals positive for MDR-TB.[26] However, one study reported a non-significant relationship between alcohol consumption and mortality in individuals with MDR-TB.[23]

Pertaining to household conditions, an association was found between substandard housing conditions and treatment default, even though socioeconomic support was provided to vulnerable patients.[27] Conversely, formal housing had a lower rate for treatment default.[32] Only one study examined the relationship between having water, a toilet, and electricity in the dwelling and default rate, however no significant relationship was found.[32] Another study found that the household size and density as well as the quality of the household structure, were unrelated to multiple MDR-TB introduction events.[33] The role of migration was not explored in depth, although one study reported that change of residential address was associated with treatment default.[31]

In terms of nutrition, some studies found that BMI estimates less than 18.5kg/m^2 (underweight for age) were significantly associated with increased mortality.[22] However, another found that the there was no significant association present for underweight/overweight/obese BMI estimates.[23] In addition, patients with MDR-TB who had a higher initial weight prior to commencement to treatment did not have a significant chance of cure.[28]

Vulnerable populations

Gender differences were reported in some of the included studies. Two studies reported that males are more at risk for TB disease than females.[25,29] Additionally, male household contacts were found to have a higher incidence of TB compared to female contacts.[29] Worth noting is that most studies included a population that was mostly represented by the male gender (>50%).[22,23,26,28,30,33] Franke et al., 2008 found a reduction in the relationship observed between female sex and death occurring after default on treatment, if certain confounders were accounted for: inadequate bacteriologic response, having been on an individualized treatment programme for less than a year, level of education, and history of psychiatric disorder. This suggests that the aforementioned factors possibly mediate the relationship existing between death after treatment default and female sex.

The included studies also highlighted the impact of HIV on the optimisation of health for individuals who are living at home with MDR-TB. Within the included studies, HIV was associated with a greater incidence of death in those with MDR-TB.[23] Conversely, some studies did not find an association for defaulting treatment in HIV positive individuals[27,32] nor a significant association between BMI and culture conversion in HIV positive individuals.[24,26] Additionally, some studies did not record HIV status within their study population, which may have had an impact on the relationship between environmental risk factors and health optimisation or transmission.[32,26,31]

Children are suggested to be particularly vulnerable if living in households with an individual who has MDR-TB. Although only three of the included studies reported on transmission to household contacts, it was found that children ≥ 2 years of age who developed TB infection were more likely to have been in contact with an adult TB source case in comparison to children who were TB-exposed but uninfected.[19] However, within the same study, children underweight for

their age did not have a significant risk of TB disease nor were more likely to have been exposed to household tobacco smoke.[19]

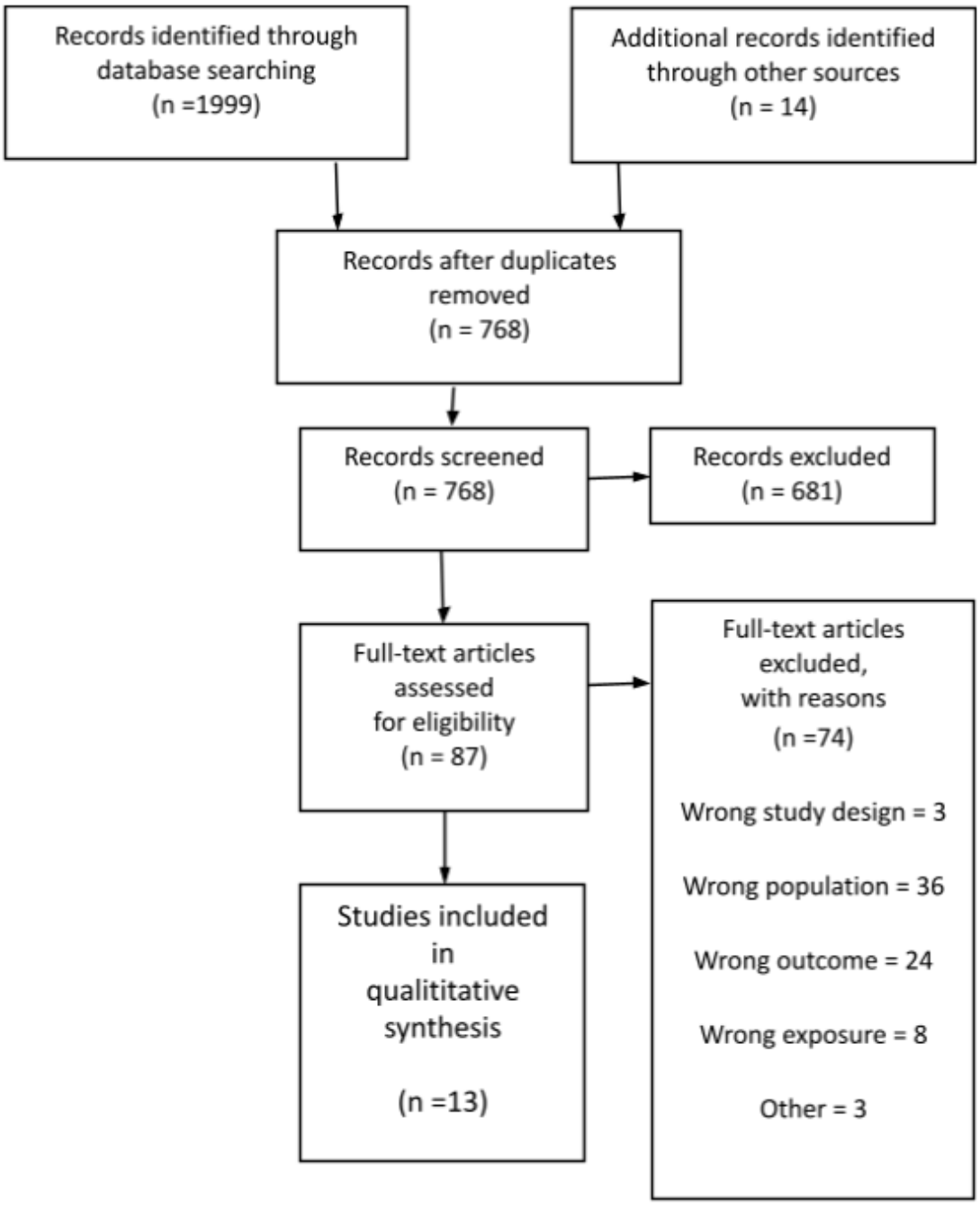

Fig. 1. PRISMA Flow diagram

Table 1: Characteristics and findings of included studies

Transmission to household contacts							
Author	**Study design**	**Country**	**Participants**	**Sample size**	**Relevant environmental health exposure**	**Outcomes**	**Main findings[1]**
Golla et al., 2017	Cross sectional	South Africa	Child household contacts older than 5 years	545 patients	Smoking, household factors, nutrition	Household contacts with TB infection and TB disease.	• Children who had TB infection were more likely to have been in contact with an adult source case [aOR* 2.05 (1.34-3.12)] • The risk for TB disease in children who were underweight for their age was non-significant [OR** 1.04 (0.56-1.92)] • Household tobacco smoke exposure was a non-significant risk factor for TB disease in children [aOR 1.22 (0.76-1.94)]
Shadrach et al., 2021	Prospective cohort	India	Household contacts of individuals with MDR-TB	271 patients	Nutrition	TB occurrence in household contacts	• Being less than 18 years of age was found to be a non-significant risk factor for TB [OR 0.72 (0.43-1.82)] • Both male sex [OR 2.3 (1.35-3.94)] as well as malnourishment [OR 1.89 (1.13-3.16)] were identified as risk factors for TB
Grandjean et al., 2011	Retrospective cohort	Peru	Household contacts of individuals with MDR-TB	2112 contacts within 358 households	Household factors	Household contacts with TB disease	• Increased risk of TB observed in male contacts. [HR# 2.82, p-value = 0.03] • No significant differences found between crowding and transmission.

Optimisation of health							
Author	**Study design**	**Country**	**Participants**	**Sample size**	**Relevant environmental health exposure**	**Outcomes**	**Main findings[1]**
Bei et al., 2018	Retrospective cohort	China	Patients aged 19–99 years with XDR-TB	72 participants	Smoking, nutrition	Mortality	● Smoking [aHR[##] 4.67 (1.66-13.16)] and BMI < 18.5kg/m^2 [aHR 4.5 (1.3-15.7)] were significant predictors of mortality.
Chung Delgado et al., 2015	Retrospective cohort	Peru	Patients aged 18 years and above with MDR-TB	1,242 patients	Alcohol, smoking, nutrition	Mortality rates; mortality associated risk factors during treatment of MDR-TB	● Non-significant factors associated with mortality: o Smoking: [HR 0.40 (0.12-1.29)] o Alcohol: [HR 0.51 (0.21-1.20)] o Body mass index: o underweight [HR 1.84 (0.97-3.50)] o Overweight/obese [HR 1.14 (0.46-2.84)]
Holtz et al., 2006	Case control	South Africa	Patients aged 18 years and older diagnosed with MDR-TB	269 confirmed cases and 401 controls	Smoking, other substance use, migration	Mortality among MDR-TB treatment defaulters	● Default of treatment was associated with the following: o Smoking marijuana or mandrax during treatment [aOR 17.9 (4.7–68.5)] o Having a place of birth outside of South Africa [OR 5.9 (1.1-32.8)] o Having a change in residence during treatment period [aOR 3.2 (1.4-7.6)]

Kendall et al., 2013	Retrospective cohort	South Africa	All patients (age > 15 years) starting MDR-TB treatment	225 patients	Alcohol, substance use. household factors	Cure or treatment completion; treatment failure, mortality	• Predictors of default during outpatient treatment: o Alcohol [aHR 2.11 (1.11-4.02)] o Drug use [aHR 2.02 (1.04- 3.95)] • Having water, toilet and electricity in dwelling was not associated with default/death or treatment failure [HR 0.63 (0.33-1.20)] • Formal dwelling was associated with a lower rate of default [HR 0.38 (0.19-0.78)]
Lu et al., 2017	Prospective cohort	China	Age group not specified. Median age = 51 years	160 patients	Smoking, alcohol, nutrition	Sputum conversion	• Risk factors affecting culture conversion: o Smoking [aHR 0.44 (0.23-0.83)] o Alcohol [aHR 0.41 (0.21-0.81)]
Franke et al., 2011	Retrospective cohort	Peru	All patients with laboratory confirmed MDR TB	671 patients	Substance use, housing, nutrition	Cure, treatment completion, treatment failure, mortality	• Substance use (unspecified) was a dominant risk factor for treatment default [aHR 2.96 (1.56-5.62)] • This finding was observed primarily among men. • Substandard housing conditions predicted treatment default [aHR 1.83 (1.07-3.11)]
Shean et al., 2008	Retrospective cohort	South Africa	Patients aged ⩾15 years initiating treatment for pulmonary MDR-TB	747 patients	Alcohol use	Cure and completion were regarded as successful outcomes, poor outcomes included death, default of treatment and failure of treatment.	• Current heavy alcohol use was associated with poor treatment outcomes [RR† 1.3 (1.02-1.7)]

Cohen et al., 2008	Retrospective cohort	Peru	MDR-TB isolates from patients in eligible households	102 households with 232 participants	Household factors	MDR-TB reinfection	• Household size, density and quality were all unrelated to multiple introduction events.
Savioli et al., 2019	Cohort	Brazil	Patients 18 years or older, with confirmed MDR-TB	190 participants	Nutrition	Initial outcome events (abandonment, failure, cure and death)	• Patients who had no comorbidities had a higher chance of cure specifically after 18-month treatment period [OR 3.37 (1.41-8.09)] • An increased initial weight did not indicate a significant chance of cure after 18-month treatment period [OR 1.04 (0.99-1.08)]
Qazi et al., 2011	Retrospective cohort	Pakistan	MDR-TB patients confirmed on culture	85 participants	Nutrition, smoking	Culture conversion	• Current smokers had a higher chance of culture conversion compared to individuals who never smoked [HR 0,08 (0,01-0,49)]

[1]Includes reported effect measure and confidence interval/p-value
*aOR = adjusted odds ratio
**OR = odds ratio
[#]HR = hazard ratio
[##]aHR = adjusted hazard ratio
[†]RR = risk ratio

Discussion

This study highlights the role of environmental health in MDR-TB prevention efforts, specifically in LMICs. Several environmental health factors including smoking, household condition, nutrition, alcohol, other substance use, urbanisation and migration were reviewed.

Smoking

Factors influencing TB, are likely to also play a role with smoking and MDR-TB.[35] Therefore, although not a new concept, it reiterates the need for improved legislation and re-evaluation of the externalities suffered by vulnerable populations who are exposed to individuals who smoke. This is especially important in LMICs, where legislation surrounding tobacco exposure may not be as stringent or protective for vulnerable populations. To address the environmental health impact of smoking, efforts towards education, a powerful tool, should be utilised. This includes individual education provided by community health workers, education in a clinical setting, and health education campaigns that bring attention to the community regarding the health impacts of smoking and MDR-TB.[16]

Substance and alcohol use

Although substance and alcohol use are not specific environmental health risk factors, they are both significant social issues, particularly in LMICs, that may have considerable influence in predisposing vulnerable individuals, even more so to environmental health risk factors. Through awareness of the impact of these factors on MDR-TB outcomes and transmission, any local or global intervention to combat TB and MDR- TB should prioritise social support in such population groups. This also extends to stricter legislation and education on the impact that other substance use and alcohol have in the context of MDR-TB.[36]

Nutrition

Nutrition has a significant impact on individuals with MDR-TB, as it is thought that poor nutrition increases the chance of TB infection and negatively impacts the immune response, making infected individuals more vulnerable to poor outcomes.[37] Strategies to address this include additional nutritional supplements, feeding programmes and improved access to dieticians and community health workers. Such programmes and interventions require intense scale-up and investment from larger stakeholders and communities, ensuring successful and sustainable programmes.[37]

Physical housing

Evaluating the impact of housing was limited to overcrowding and personal habits of individuals (i.e. tobacco exposure), rather than physical attributes of households. In addition, different types of cooking sources, which have been described in previous studies evaluating general TB risk, were not explored within the included studies.[38] Furthermore, the link between MDR-TB outcomes, transmission incidence, and air pollution was not described. Thus, it is unclear what the relationship is between MDR-TB transmission and households using different fuel sources, or households that are close to outdoor air pollution sources. The evaluation of housing conditions and MDR-TB also identified vulnerable populations. Children living in households with MDR-TB positive individuals, may be particularly vulnerable to transmission in poor housing structures, due to their known vulnerability to environmental exposures.[39]

Gender Vulnerabilities

As mentioned, previous research has reported gender vulnerabilities in TB, where males were identified as having a higher risk of acquiring TB particularly, in LMICs.[6,40] Conversely, women are potentially exposed to greater amounts of indoor air pollution, using solid fuel for cooking purposes thus placing them at higher risk.[38] This controversy and lack of gender-disaggregated data warrants further investigation as the consequences thereof are important in the achievement of SDGs grounded in gender equality (SDG 5), as well as for prioritization of vulnerable gender groups in national health strategies targeting MDR-TB. This is a clear gap in current research which warrants further investigation.

Migration and Urbanisation

This review was unable to draw any firm conclusions regarding the role of migration and urbanisation due to limited evidence available. Both are complex themes which are under considerable socioeconomic and environmental influence. Thus, a conclusion regarding their influence in optimising health outcomes as well as transmission prevention requires further investigation. Urbanisation, in particular, may have significant influence on an individual's access to housing, type of housing structure and household crowding. It may also increase migration for job opportunities, as well as adapt available nutritional resources.[16] These complex themes require further research to fully understand their influence in MDR-TB prevention.

Policy implications

This review highlights important considerations for policy and decision making in LMICs. Firstly, the role of environmental health can be incorporated into actionable objectives to attain local as well as global policy goals. The SDGs are examples whereby the role of the environment and its impact on health should be prioritised in addressing the management of MDR-TB.[15] Secondly, local and national health guidelines developed for the prevention and management of MDR-TB should recognise and include relevant steps in providing environments that are conducive to health. This will allow health decisions to be made in a comprehensive manner, with the environment as a key consideration in the prioritisation of an individual's health and fulfillment of basic human rights. Thirdly, identified vulnerable populations (e.g. gender groups, children and HIV positive populations) should be prioritised in local and global policies addressing the management and prevention of MDR-TB. This is imperative to tackle the injustice and inequality that exists for such groups. Finally, the role of stakeholder engagement and investment is critical to addressing environmental health issues in the context of MDR-TB management and prevention.

There are limitations to this study which can be attributable to the nature of the primary data obtained in the review process. Due to the heterogeneity of the primary data, as well as results of the quality appraisal, interpreting the results should be done with this consideration. The quality of studies included varied significantly. In addition, the results may have been influenced by unidentified confounding variables or by inappropriate strategies to address missing data caused by loss to follow up. Most studies included data which relied on self-report thus could be significantly impacted by recall bias. Some studies also relied on a convenience sampling method; therefore, the results may be prone to selection bias, potentially impacting the generalisability of the results. In addition to the complexity of the subject matter, search terms

may have oversimplified major themes such as urbanization and migration. This may have resulted in the underrepresentation of the role that poverty and the effect thereof may have in the outcomes of MDR-TB treatment. Therefore the complexity of these themes should further be critically analysed in future work. Due to the lack of available data pertaining to the subject, interpretation of the results cannot be done with full confidence unless further data becomes available. However, the results do provide a platform for this gap in research to be highlighted and also provides motivation for future research. Finally, limiting studies in this review to those published in English may also have neglected to identify potentially relevant research.

Conclusion

The results of this review highlighted the potential relationship between environmental risk factors and optimising the health of individuals living in the community with MDR-TB, as well as the role that environmental health may play in preventing the transmission of MDR-TB to household contacts. Local and global policies including WHO targets and SDGs, should emphasise the environment in strategies to provide actionable goals in improving the health of individuals with MDR-TB, as well as to prevent transmission to exposed household contacts. Further research regarding environmental risk factors in MDR-TB transmission and optimisation of health, should provide greater certainty and understanding of the influence of the environment in MDR-TB to strengthen policy making and prevention efforts.

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PART C: Appendices

Appendix 1: Data extraction sheet

Environmental health recommendations for Multidrug-Resistant Tuberculosis in low- to middle-income countries: a systematic review			
Study identifiers			
Reviewer's initials/name			
Study ID			
Study title			
First author			
Publish date (year)			
General information			
Date of form completion (dd/mm/yyyy)			
Citation reference			
Language			
Author contact details			
Journal			
Publication type:	Abstract □	Full report □	Other □ _____

References of other potential studies selected from reference list	
Additional information	

Study characteristics					
Study inclusion/exclusion criteria					
Study design	Retrospective cohort □	Prospective cohort □	Case Control □	Cross-sectional	Other □ _____
Study type	Quantitative □	Qualitative □		Mixed Methods □	
Study setting	Clinic □	Hospital □	Community □	Other □ _____	
Initiation date of study					
Country					
Sampling method					
Participant group					
Participant group mean age					
For cohort- selection of non-exposed	Same source as exposed □	Drawn from different source □	No description of derivation □		
For case control – selection of non-diseased					
For cross-sectional selection-selection of group					
Study inclusion criteria					

Study exclusion criteria					
Exposure and outcome data					
Exposure assessment: Environmental health risk factor					
Method used for assessment of risk factors	Self report□	Screening Tool□ _____	Other □ _____		
Authors definition of risk factor					
Exposures investigated:					
Home condition	Overcrowding □	Ventilation□	Sanitation □	Other:_____	
Socioeconomic factors	Alcohol use □	Urbanization □	Migration □	substance abuse □	Other_____
Nutrition					
Air Pollution	Indoor □	Outdoor □	Other _____		
Vulnerable group	Gender	Children	HIV/Aids	Other_____	
Outcome diagnosis: MDR-TB					
Setting of diagnosis of MDR-TB					
Authors definition of MDR-TB					
MDR-TB assessment	Self report□	Screening Tool□ _____	Other □ _____		
Setting of assessment of MDR					
Sample size/Loss to follow up					
Sample size at initiation of study					

Loss to follow up					
No. Lost					
No. Died					
Other					
Final sample size (N)					
Time to follow up					
Outcome summary statistics: MDR-TB					
Outcome of interest not present at start of study	Yes □	No □	Not disclosed □	N/A □	
Relative measure of association type	Odds Ratio (OR) □	Prevalence ratio (PR) □	Risk Ratio/Relative Risk (RR) □		
Home condition	Overcrowding □ RR/OR/PR Confidence Interval: P-Value:	Ventilation □ RR/OR/PR Confidence Interval: P-Value:	Sanitation □ RR/OR/PR: Confidence Interval: P-Value:	Other:_____	
Socioeconomic factors	Alcohol use □ RR/OR/PR: Confidence Interval: P-Value:	Urbanization □ RR/OR/PR: Confidence Interval: P-Value:	Migration□ RR/OR/PR: Confidence Interval: P-Value:	Substance abuse □ RR/OR/PR: Confidence Interval: P-Value:	Other_____ RR/OR/PR: Confidence Interval: P-Value:
Nutrition	Describe: RR/OR/PR: Confidence Interval: P-Value:				

Air Pollution	Describe: RR/OR/PR: Confidence Interval: P-Value:			
Vulnerable group	Gender□ RR/OR/PR: Confidence Interval: P-Value:		HIV□ RR/OR/PR: Confidence Interval: P-Value:	Children□ RR/OR/PR: Confidence Interval: P-Value:
Missing data				
Confounders adjusted for (list all)				
Further clarification (list entry)				
Final inclusion/exclusion	**Include □**	**Exclude □**	**Uncertain □**	**Awaiting third party confirmation □**
Clarify reasons for exclusion, uncertainty or third party correspondence				

Appendix 2: Quality appraisal of final included sample

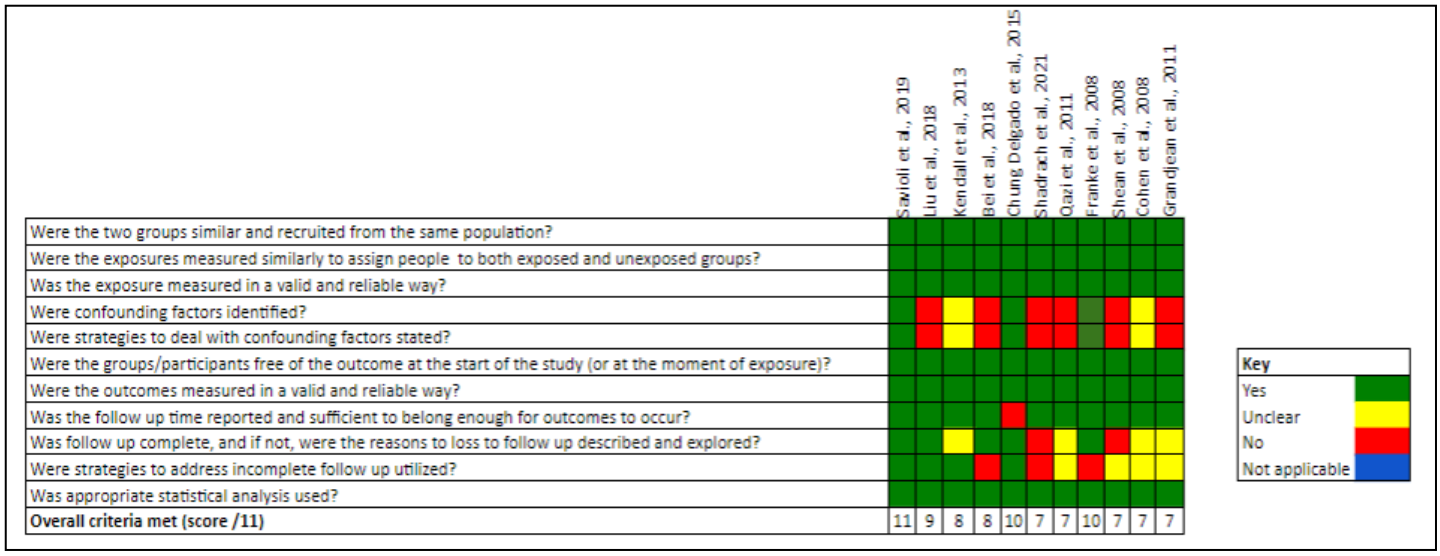

Fig. 2. Quality appraisal for cohort studies

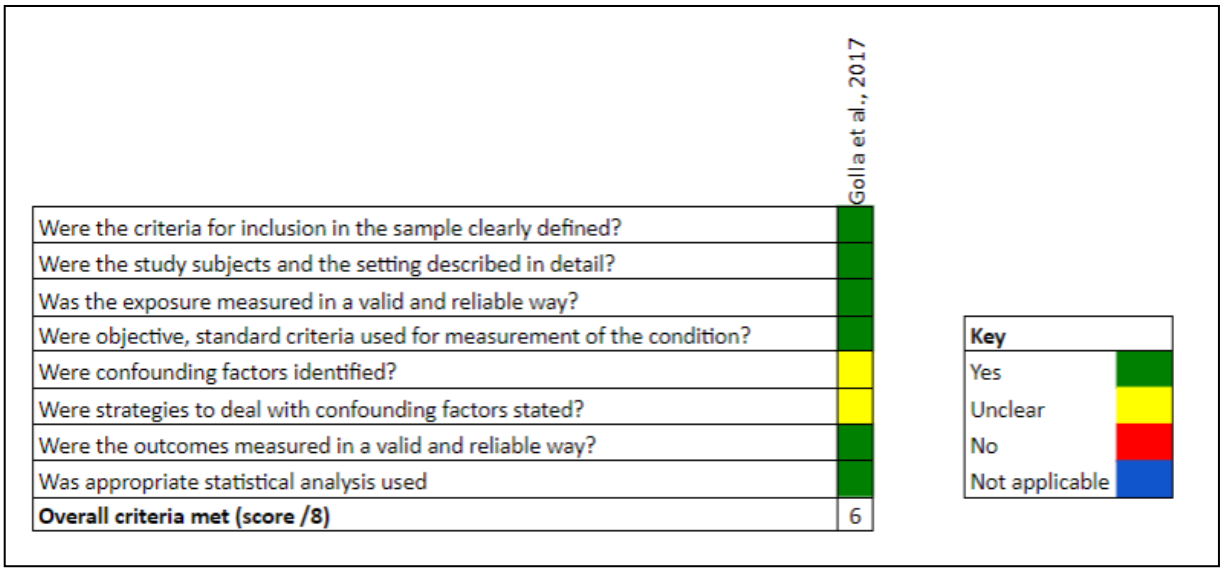

Fig. 3. Quality appraisal for cross sectional study

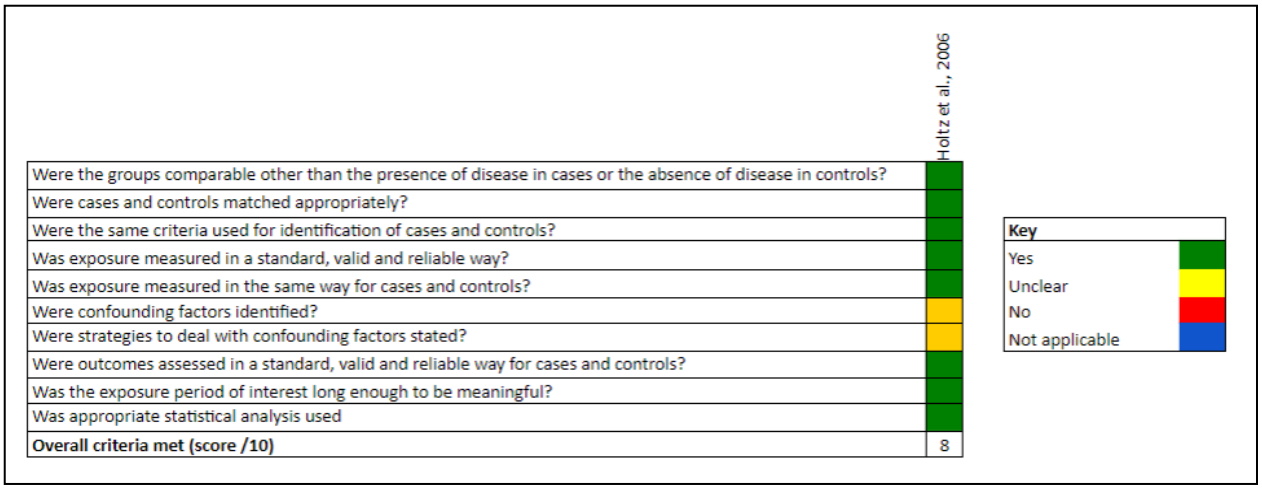

Fig. 4. Quality appraisal for case control study

Annexure A: South African Medical Journal Author guidelines

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.

Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

Manuscripts must be written in UK English.

The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).

Please make your article concise, even if it is below the word limit.

Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).

Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

Human Gene Mapping Workshop (HGMW): genetic notations and symbols

HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature

OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

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CME

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Reviews

Clinical trials

Correspondence

Obituaries

Book reviews

Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

This should be 250-400 words, with the following recommended headings:

Background: why the study is being done and how it relates to other published work.

Objectives: what the study intends to find out

Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

Conclusion: must be supported by the data, include recommendations for further study/actions.

Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.

Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed

Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.

Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.

Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

Start with description of the population and sample. Include key characteristics of comparison groups.

Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.

Do not replicate data in tables and in text.

If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:

E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).

Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

Statement of principal findings

Strengths and weaknesses of the study

Contribution to the body of knowledge

Strengths and weaknesses in relation to other studies

The meaning of the study – e.g. what this study means to clinicians and policymakers

Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

expert opinion

personal clinical experience

observational studies

trials

systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).

If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

Each article requires an abstract of ±200 words.

The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

case report

Clinical practice

Clinical alert

Issues in medicine

Issues in public health

Healthcare delivery

Medicine and the environment

Medicine and the law

Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.

Short abstract: does not need to be structured, but should capture the essential features of the article

Introduction: the reason for the article and the issue being addressed

Recent research, discussion, local policy around the issue – include your own research where appropriate

All statements should be referenced and, if opinion only, this should be stated

Discussion: how this article adds to the discussion around a particular topic

If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

Title of case: do not include the words ‘a case report’ in the title

Summary/abstract: up to 150 words summarising the case presentation and outcome

Background: why is this case important and why did you write it up?

Case presentation: presenting features, medical, social, family history as appropriate

Case management: should be according to best practice, and if not, please explain why

Investigations, if relevant: save space by simply saying ‘normal’ if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant

Differential diagnosis, if relevant

Treatment, if relevant

Outcome and follow-up

Discussion – a VERY BRIEF review of similar published cases

Teaching points: 3 - 5 bullet points

References: as per the *SAMJ* house style

Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form

Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.

Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

May include only one illustration or table

Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).

All images must be of high enough resolution/quality for print.

All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.

Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.

Scans/photos showing a specific feature e.g. Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain). –include an arrow to show the tumour.

Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.

Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author

Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.

Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

Ensure each table has a concise title and column headings, and include units where necessary.

Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must **not** be used.

Authors must verify references from original sources.

Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).

Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.

Volume and issue numbers should be given.

First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

On the Crossref homepage, paste the article title into the 'Metadata search' box.

Look for the correct, matching article in the list of results.

Click Actions > Cite

Alongside 'url =' copy the URL between { }.

Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: Publisher name, year; pages.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.