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The Effect of Digital Health on Patient Care in Tuberculosis Patients from Low and Middle-Income Countries

A Systematic Review

Minor Dissertation In partial fulfilment of the requirements for the degree:
Master of Philosophy in Health Innovation

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Declaration

I, Jacobus Johannes Le Roux, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background

LMICs account for approximately 87% of all new TB cases. Effective TB management is vital if the global end TB goals are to be achieved by 2035. The role of digital health (DH) interventions in achieving these goals are pertinent. TB treatment adherence is considered to be critical not only in successful eradication of the disease, but also in the containment of drug-resistant strains of the disease. This review set out to assess the effect of DH interventions on TB patient treatment adherence in LMICs.

Methods

A systematic review was conducted by searching various databases (Pubmed, Scopus, EBSCOhost Web of Science) as well as grey literature sources for literature incorporating randomized controlled trials (RCTs), cohort, or cross-sectional studies which assessed DH interventions aimed at improving TB patient treatment adherence within LMICs. Studies were included if they were reported primary outcomes related to patient treatment adherence and were published in English before 30 November 2020. The risk of bias was independently assessed using the Cochrane Risk of Bias Assessment Tool.

Results

Out of the 1030 articles identified through the databases, 41 articles were full text screened and eleven included in the synthesis of this review. Seven studies utilized text-based reminders, two employed electronic medication monitors, and two employed call reminders, and one involved video observed therapy (VOT). Grouped analysis of all included studies yielded a marginal improvement in positive patient treatment outcomes (RR 1.05, 95% CI 1.02 - 1.09).

Conclusion

DH interventions show promise in improving patient adherence and positive treatment outcomes. Current available literature remains scarce and of questionable quality. Studies incorporating a patient-centred approach which is executed according to standardized implementation procedures and outcome assessment is required.

Acknowledgements

I would like to firstly acknowledge my supervisor, Dr Jill Fortuin who throughout this whole process remained patient, kind, and consistently helpful, even though the circumstances under which this review was written have been tumultuous.

I would also like to acknowledge my family who have supported me from afar, and those close to me, for the undying love and encouragement throughout this process.

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Glossary of Terms

List of Abbreviations

ART	Anti-retroviral therapy
CI	Confidence interval
DH	Digital health
DOT	Directly observed therapy
eHealth	Electronic health
EMM	Electronic medication monitor
HIV	Human immunodeficiency virus
JF	Jill Fortuin
JLR	Jannes Le Roux
LMIC	Low- and middle-income country
MeSH	Medical subject heading
MDR-TB	Multidrug-resistant TB
mHealth	Mobile health
MTB	*Mycobacterium* tuberculosis
PTB	Pulmonary TB
RCT	Randomized control trial
RR	Risk ratio
SMS	Short message service
TB	Tuberculosis
UN	United Nations
VOT	Video observed therapy
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

List of Definitions

Outcome	*Definition*
Cured [i]	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed [i]	A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed [i]	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died [i]	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up [i]	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated [i]	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success [i]	The sum of cured and treatment completed.
Digital Health[ii]	A collective term for eHealth and mHealth technologies.

[i] Standard definitions as per WHO Definitions and Reporting Framework for Tuberculosis (WHO, 2013)

ICT[ii]	The means employed to provide access to information through internet, wireless networks, mobile phones and other communication or media channels.
eHealth[ii]	*The cost-effective and secure use of information and communication technology (ICT) for health and health-related fields.*

[ii] Standard definitions as per WHO Digital Health End-TB Strategy (WHO, 2016)

1. Introduction

Tuberculosis (TB) remains among the top 10 causes of death worldwide, accounting for an estimated 1.4 million deaths in 2019 alone (WHO, 2020). Despite the disease being curable and preventable, an estimated 10 million people contracted the disease in 2019, bringing the total amount of infected individuals to an estimated 1.7 billion (WHO, 2020). The epidemiology of MTB varies significantly globally, with the highest disease burden being disproportionately focused on developing, low- and middle-income countries (LMICs) which accounts for 87% of all new TB cases, along with over 95% of all TB related deaths (WHO, 2018). Within these resource-limited settings, strained healthcare systems fail to effectively diagnose, treat, and manage TB patients. Co-morbidities (like HIV), poverty, and drug-resistant strains of MTB have severely destabilised disease control in developing nations (Wright et al., 2009). Effective treatment of multi-drug-resistant (MDR-TB) and extensively drug (XDR-TB) resistant strains have proven to be costly and resource demanding, adding additional pressure to economies and infrastructure in LMICs where the disease is most prevalent (Kurz et al., 2016; Pooran et al., 2013).

The United Nations (UN) and World Health Organization (WHO) have outlined strategies aimed to reduce TB deaths and new cases by 95% and 90% respectively between 2015 and 2035 (WHO, 2016). Highlighted as one of the principal resources in the WHO agenda to end TB, is the utilization of digital health (DH) solutions in the fight against TB (WHO, 2016). This notion is predicated on data indicating a rapid increase in technological access and interconnectivity seen in developed and developing nations alike, with the International Telecommunications Union (ITU, 2018) estimating that 51.2% of the global population were accessing the internet at the end of 2018. Access to- and use of information and communication technology (ICT) has laid the foundational groundwork which has given rise to the development and implementation of mobile health (mHealth) initiatives aimed at improving existing healthcare service delivery in rural or resource-limited settings (Tamrat & Kachnowski, 2012).

Even though the amount of DH solutions in high-income countries (HICs) have been shown to be significantly higher than in LMICs, DH initiatives in LMICs have rapidly increased over the last decade. Within LMICs, DH initiatives have been shown to target health monitoring, surveillance, and health promotion (AbazaHaitham & Marschollek, 2017). Many of these interventions have shown considerable potential in multiple applications: Electronic data capture in Malawi have

showed to be both efficient and scalable (King et al., 2014). In Ghana, the community-based hypertension improvement programme (ComHIP) proved itself as a valuable resource in educating end users and raising awareness of hypertension (Lamptey et al., 2017). SMS messages as a method to improved ART treatment adherence in Kenya showed significantly higher adherence in the intervention cohort (R. T. Lester et al., 2010).

A principal component of positive patient outcomes is uninterrupted treatment adherence (Nahid et al., 2016; WHO, 2019). Prolonged duration of treatment (usually 6 months and longer) paired with a combination of different therapies have rendered uninterrupted treatment completion a challenge to many. In many LMICs, efforts to promote treatment adherence through programmes such as directly observed therapy (DOT) have presented with inconsistent success, attributing treatment failure in LMICs to lack of resources and socio-economic factors rather than treatment availability (Karumbi & Garner, 2015). DH solutions aimed at overcoming these barriers could prove vital in improving treatment adherence. Considering the importance of treatment adherence, this systematic review will assess available literature with studies that report on TB patient treatment adherence as influenced by DH interventions.

1.1 Aims and Objectives

The following research question will be addressed: How does digital health impact treatment adherence in the TB patient care pathway?

The Participant Intervention Comparator and Outcome (PICO) model for this review includes the following:

P/Participants: TB Patients from low- and middle-income countries

I/Intervention: DH intervention serving as a reminder

C/Comparator: Routine practice

O/Outcome: Treatment adherence or any reported outcome which could serve as a proxy

The aim of this study is to conduct a systematic review of literature to determine the impact of DH interventions on the care pathway of TB patients

Objectives for this systematic review include:

1. Assess the penetration of DH initiatives which influence TB patient treatment adherence in LMIC to determine whether DH solutions improves patient outcomes
2. Review and understand factors either impeding or promoting the positive effect of DH on TB patient health outcomes

1.2 Outline

The outline of this dissertation is as follows:

Section 1 elucidates the relevant background information pertaining to TB, its global impact, and the disproportionate TB burden in LMICs. Additionally, it elaborates on the emergence of connectivity and the subsequent integration of health services and technology. This section also contains the aim, research question, PICO statement, and objectives of the study.

Section 2 presents the available literature which is relevant to TB, LMICs, and DH. This section explains why the TB burden is focused in LMIC regions by identifying and elaborating on the various determinants of TB patient treatment outcome. Section 2 also reviews available literature on cases where DH solutions have been implemented. This section outlines the TB patient cycle of care, and the various characteristics influencing patient outcome.

Section 3 explains the systematic review methodology utilized in this study. This section describes the search strategy, eligibility criterion, study selection protocols, and well bias mitigation strategies.

Section 4 presents the results attained following the processes and steps outlined in section 3.

Section 5 discussion the implications of these results, the limitations of the study, and concludes with recommendations informed by the results from this review.

2. Literature Review

This section reviews the existing literature relating to tuberculosis, LMICs, and DH. It elaborates on TB as a disease state, the importance of treatment adherence in the TB care pathway, the differences in TB patient outcomes witnessed between developed and developing countries, and the disease predictors. This section reviews the WHO handbook for DH interventions affecting patient adherence. Furthermore, this section outlines examples of past and existing DH solutions, both related to TB and similar diseases.

2.1 Participant/Subject Area (TB)

Mycobacterium tuberculosis (MTB) was first discovered by Dr Robert Koch in 1882. Diagnosis of this disease once meant certain death. Today, more than a century later, the effect of TB on global health remains severe, with the WHO (2020) reporting a disease incidence of 10 million people in 2019, along with 1.4 million TB related deaths in the same year. Consequently, TB is currently ranked as the number one leading cause of death among infectious diseases.

MTB is an intracellular microorganism which spread via aerosol droplets. Once these particles are inhaled, one of four possible outcomes occur:

1. Immediate clearance of the MTB by the immune system
2. Development of primary disease (immediate onset of active disease)
3. Latent infection
4. Reactivation disease from latent infection

The particular outcome which a patient presents with is influenced by a range of factors. In the case of primary disease development, the patient develops symptoms ranging from mild coughing and fever to complete respiratory failure. TB commonly manifests in the lungs (pulmonary TB) but can also manifest outside of the lungs (extra-pulmonary TB). Pulmonary TB is characterised by the MTB bacilli infiltrating the alveoli in the lungs and consequently infecting and destroying alveolar macrophages causing chronic inflammation. Studies examining TB transmission-dynamics highlights a range of factors which contribute to disease spread, most notably source infectiousness, environment, exposure, and potential host susceptibility (Turner et al., 2017).

Diagnosis

TB diagnosis is expected in patients presenting with the relevant symptoms in areas where TB is endemic. TB diagnosis can be aided by radiographic imaging or by microbiological testing. A patient can only definitively be diagnosed with TB once a sample specimen is collected and analysed from the relevant patient and analysed for MTB. Sputum acid fast bacilli (AFB) smear microscopy is the most inexpensive and rapid form of TB diagnosis. Though fast and cost-effective, this technique lacks both sensitivity and specificity where the former have been shown to range between 45 to 80 percent, and the latter ranging from 50 to 80 percent (American Thoracic Society, 2000). More accurate results can be attained by culturing the collected sample in culture media, however mycobacterial cultures take up to three to eight weeks to grow. The most modern diagnostic advancements include molecular testing such as nucleic acid amplification. These tests are rapid and accurate, but expensive. The cost and infrastructure required for this diagnostic technique renders it inaccessible for the majority of LMICs, especially in rural areas.

Treatment

Once a patient is diagnosed with active TB, a treatment strategy can be initiated. The WHO endorses directly observed therapy (DOT), a 6-month multidrug treatment regimen for TB patients aimed at maximizing patient adherence and subsequent therapeutic success by proposing in clinic or at home observation of a patient taking their medication for at least the first two months of treatment. Factors such as treatment quality and immune status affects treatment success, with treatment adherence being credited with the most significant impact on TB patient outcomes (Keng Tok et al., 2020; Tesema et al., 2020). The WHO estimates that approximately 85% of all TB diseased patients can be effectively treated with a 6-month treatment regime (WHO, 2020). Regrettably, treatment success is crippled by poor adherence and drug quality, which requires patients to be retreated. Retreatment consists of a lengthier, more potent, and disruptive treatment regime (Keng Tok et al., 2020). The development of drug-resistant strains of MTB are even more costly and challenging to treat. Treatment strategies targeting MDR- and XDR-TB have a longer duration and contain higher doses of anti-TB drugs.

Epidemiology

Two thirds of the global TB burden are reported to be concentrated within eight countries namely: India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa (WHO, 2020). Furthermore, the WHO (2018) estimates that over 95% of TB deaths occurring exclusively in LMICs. Conversely, developed nations such as the United States of America (USA) reported an incidence of 10 000 new cases in 2018 (WHO, 2018). Studies assessing the disproportionate burden of TB in LMICs stress the impact of socio-economic factors such as poverty, co-morbidities like HIV, and drug resistance on the prevalence of TB (Corbett et al., 2006; Wright et al., 2009). It is estimated that 1 in every 9 cases of TB occurs as a co-morbidity with HIV (WHO, 2018). Social and economic determinants in TB incidence have been reported to have a principal impact in disease eradication, with more developed regions showing a decline in TB incidence even among an absence of quality TB treatment. The contrary is witnessed in regions with robust treatment programmes paired with a lower social economic status (Dye et al., 2009). These findings reinforce the notion that socio-economic factors retain a critical role in TB disease control efforts.

LMIC and TB

The disparity in TB morbidity between LMIC and their more developed counterparts is attributed to a range of factors. It is well reported that the socio-economic status of an individual affects their susceptibility to TB. Disease progression from exposure to active TB infection is primarily affected by three factors: source infectiousness, degree of exposure, and host susceptibility (Lienhardt, 2001). Socio-economic determinants such as poverty, co-morbidities, and lack of access to quality healthcare have shown to greatly increase the burden of TB (Corbett et al., 2006). Additionally, population density, malnutrition, and race have also been shown to exacerbate the TB burden (Lienhardt, 2001). These characteristics are all common in developing regions and LMICs.

Two aspects severely plaguing TB control are access to- and early diagnosis for at-risk patients, as well as a lack in therapeutic monitoring. Patients in more rural environments bear the brunt of these effects. Residents in LMIC who reside in densely populated areas are plagued by high TB transmission rates. Furthermore, in countries where healthcare resources are limited, patients are likely to receive sub-optimal and variable care (Kwan et al., 2018). Lack of adequate treatment and disease management laid the foundation for the emergence of drug resistant strains of MTB,

which require exorbitantly expensive and labour-intensive treatment, often leading to financial ruin for the affected patient (Tanimura et al., 2014).

The World Bank classifies countries based on the Gross National Income (GNI) per capita. Economies are classified into Low-income-, lower-middle-income-, upper-middle-income- and high-income economies. The eight highest TB-burdened countries (India China Indonesia the Philippines Pakistan Nigeria Bangladesh and South Africa) all fall within the LMIC GNI bracket (The World Bank, 2020).

The United Nations (UN), in collaboration with the WHO, have pledged their collective allegiance to ending the global TB epidemic by 2030 (United Nations, 2015; World Health Organization, 2015). Additionally, National TB Programmes (NTP's) aim to decrease the TB burden on a national level by supplying the required diagnostic, treatment, and preventative services required by the TB patients of their respective nations. NTP's allows for a framework which hold countries accountable in their respective pursuit toward eradicating TB. Even though the latest Global TB Report by the WHO (2020) does report a slight decrease in TB incidence over the last year, it confirms that progress being made is insufficient in reaching the goals set out in the End TB Strategy. The lack of progress has resulted in a shift of focus to emerging and innovative solutions in addressing the global TB burden such as DH initiatives.

2.2 DH for disease management

Digital health (DH) is defined by the WHO (2016) as *"The cost-effective and secure use of information and communication technologies (ICTs) for health and health-related fields".* Over the last decade, global connectivity has experienced unprecedented growth. More than 57% of the world's population have access to internet connectivity, with 3G or above mobile broadband coverage reaching 84% of the global population, and 67% of the rural population (ITU, 2018). This unprecedented growth in global connectivity have been foundational in reshaping the ways in which healthcare delivery is taking place, especially within LMIC.

DH interventions have shown potential in affecting healthcare delivery in LMIC. In many cases, these solutions have been observed to positively affect patient adherence to disease treatment, as well as monitoring and diagnosis (Brunetti et al., 2018; Ivanova et al., 2019; Nsengiyumva et al.,

2018; Wood et al., 2019). The WHO recognizes the potential of DH solutions and have established The Global Task Force on digital health for TB. The group consists of experts in both TB care and information and communication technology (ICT) who are tasked with promoting DH applications use in countries in the pursuit of ending TB (World Health Organization, 2015). The WHO have provided a framework for classifying DH interventions. This framework aims to group DH solutions based on function and is represented in Table 1 with data adapted from (WHO, 2015).

*Table 1: The Four Functional Categories and Associated Potential Application for DH Solutions in TB Care**

Functional Category	Description with Potential Applications
Patient care and electronic DOT	DH interventions focusing on alternatives for DOT, medication adherence monitors, and patient treatment adherence reminders
Surveillance and Monitoring	Reporting infrastructure for announcing patient episodes and feedback, including the mapping of geographical patient data
Programmatic Management	DH solutions aiding in equipment and medication stock monitoring and management, electronic patient records, and notification of patient comorbidities
eLearning	Educational resources and tools which could aid in promoting patient health and wellbeing, as well as treatment guidelines.

**Table adapted from: World Health Organization & European Respiratory Society. (2015). Digital health for the end TB strategy: an agenda for action. World Health Organization. https://apps.who.int/iris/handle/10665/205222*

Types of Interventions and Associated Challenges

Intervention types vary depending on the target profile and nature of the intervention. Electronic Medication Monitors (EMM) are electronic medicine containers which monitor and reports when the container is opened. When medication containers remain unopened, the healthcare provider is notified, and appropriate follow-up procedures would take place to ensure adherence.

Text message reminders are text-based communications which are sent to patients to remind them to take their medication. One-way text-based medications require no response from the patient on whether they received the message. Two-way, or interactive reminders require patients to respond to the text reminder, confirming that they received the communication and adhered to taking their medication. Phone calls are included in interactive reminders.

Video observed therapy (VOT) or electronic directly observed therapy is a digital observation solution and alternative for DOT. This solution aims to reduce patient travel cost and inconvenience. It is also a safe method, as the patient is not required to visit the clinic to comply with their treatment regime. This minimizes the potential for disease transmission.

These DH adherences all require basic infrastructure to function. Most notably, access to a cellular phone, and to broadband internet. The WHO (2017b) asserts that VOT necessitates is the most resource-intensive, while SMS and cellular phone calls require minimal access to reliable broadband internet and does not require patients to have of use a smartphone. Another disadvantage which these devices pose in its intrusiveness in the lives of patients. The rigorous oversight on patient adherence which these devices supply is seen as an ethical dilemma by many (WHO, 2017a).

The TB Patient Pathway and DH

The WHO (2018) have published a handbook which outlines implantation guidelines and pitfalls. This document highlights the importance of DH solutions which should be built on existing infrastructure, healthcare resources, and policies within the environment. This requires that solutions be tailored and carefully analysed prior to integration. Failure to conduct a thorough preliminary assessment of the feasibility of a solution would likely result in a waste of resources, or redundant systems (Denkinger et al., 2013).

In their guide to implementing DH initiatives which aids in TB patients' treatment adherence, the (WHO, 2017b) features a patient pathway which is adapted from the KNCV Tuberculosis Foundation (KNCV, n.d.). This pathway illustrates the interactions and intervention points within the patient care pathway which can be improved by the various categories of DH solutions outlined in Table 1 is featured in Figure 1.

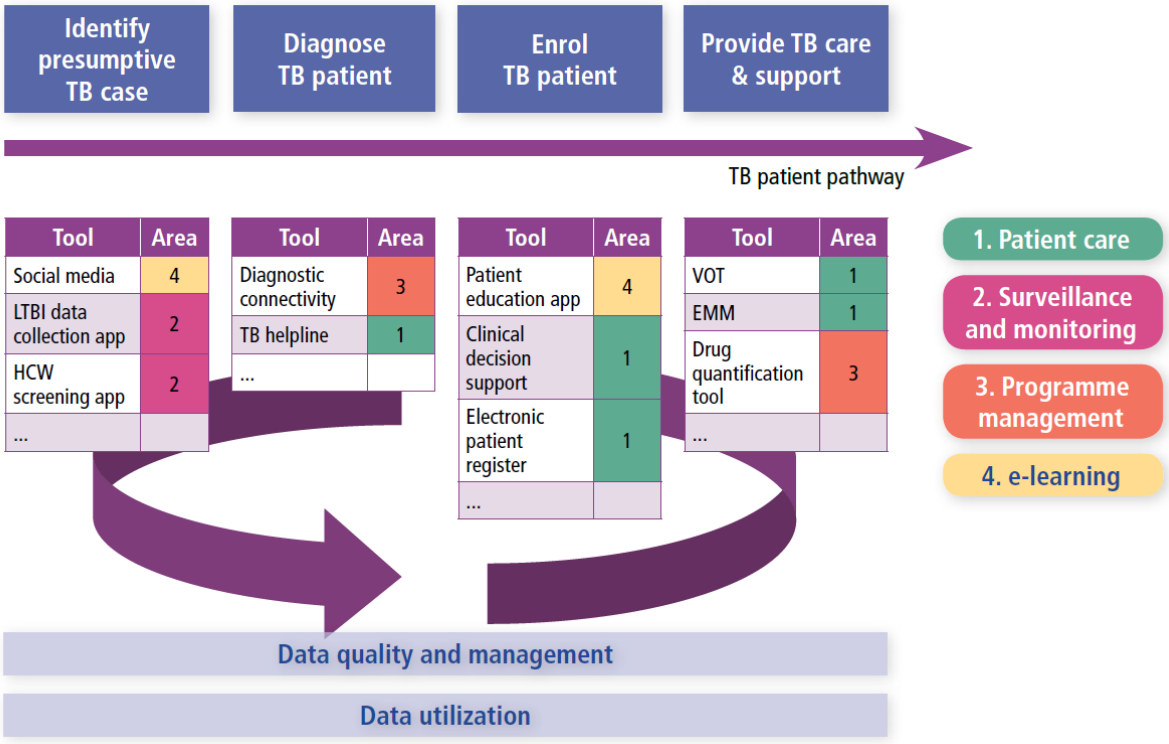


Figure 1 TB Patient Care Pathway with Associated DH Intervention Integration. Adapted from: Handbook for the use of digital technologies to support tuberculosis medication adherence. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Outcomes assessed in this review are treatment adherence, and treatment outcome. Treatment outcome is defined by a reporting framework developed by the WHO (2013). This includes patients cured, treatment completed, treatment failure, patient death, loss to follow-up, and treatment success. Treatment adherence is assessed by outcome measures including doses observed, medication adherence, and doses missed.

3. Methods

This chapter describes the various steps which was taken to conduct this review. The methodology of this review is in accordance with the Cochrane Handbook of Systematic Reviews for Interventions (Chandler et al., 2017)

3.1 Protocol and Registration

The systematic review protocol has been registered with the International Prospective Register of Systematic Review, also known as PROSPERO. The PROSPERO registration number: CRD42020213474.

3.2 Eligibility Criteria

3.2.1 Study Design

This systematic review will review quantitative studies. Study design includes randomized control trials, non-randomized controlled trials, cohort studies, case-control studies and cross-sectional studies.

3.2.2 Study Participants

Participants included will include all patients suffering from active pulmonary or extra-pulmonary TB in LMIC, regardless of race, gender, or religion.

3.2.3 Study Setting

This review will include DH solutions sited in low- and middle-income countries. The World Bank categorises these countries as having a gross national income (GNI) of $ 1,026 - $3,995 for lower-middle-income economies, and a GNI of $3,996 – 12,375) for upper-middle-income countries (Fantom & Serajuddin, 2016).

3.2.4 Types of Intervention

Interventions included in this review will involve existing, as well as past DH initiatives which are aimed at improving patient treatment adherence.

DH within the context of this systematic review refers collectively to mHealth and eHealth interventions, including all mobile technologies and ICTs used in health and health-related fields.

3.2.5 Outcomes

The primary outcome will assess the effect of existing DH solutions on the TB patient treatment adherence. Reported outcomes of treatment success, patient adherence and unsuccessful treatment will serve as proxy to assess DH intervention efficacy.

3.3 Search Strategy

Relevant studies were identified within the period starting in 1993 (when DH and eHealth first emerged in literature) through to 31 Augustus 2020. The language of publication and subjects of study will be limited to English and humans, respectively.

Databases included in the search: PubMed, Scopus, Web of Science. Literature from sources including PubMed, Scopus, CINAHL, Africa Wide Information, Computers & Applied Sciences Complete, Health Source: Nursing/Academic Edition by EBSCOhost, as well as Web of Science will be assessed. Additionally, grey literature sources will be assessed for unpublished data that are relevant to the study.

Studies was identified by utilizing a predefined search term strategy which was developed in collaboration with the UCT Health Sciences Library. The search strategy was based on relevance to term of study. Searches on different databases was modified accordingly to suite the particular database. The search strategy is based on the PICO criteria, with relevant terms including free text, Medical Subject Headings (MeSH) and Boolean operators. An example of the search strategy used to search the Pubmed database in outlined below in Table 2. The comprehensive search strategy can be found in **Appendix i.**

Table 2 Pubmed search strategy with included search results conducted 20 August 2020

Population: Tuberculosis			
#1	MeSH terms:	"tuberculosis"[MeSH]	192 815
#2	Free text:	tb or tuberculosis or mycobacterium tuberculosis or mtb or Kochs disease OR Koch's Disease OR Koch Disease OR Multidrug-resistant Tuberculosis OR MDR tb	301 499
#3	#1 OR #2		301 499
Population: LMIC			
#4	MeSH terms:	"developing countries"[MeSH]	75 306
#5	Free text:	Deprived Countries OR Deprived Population OR Deprived Populations OR Developing Countries OR Developing Country OR Developing Economies OR Developing Economy OR Developing Nation OR Developing Nations OR Developing Population OR Developing Populations OR Developing World OR LAMI Countries OR LAMI Country OR Less Developed Countries OR Less Developed Country OR Less Developed Economies OR Less Developed Nation OR Less Developed Nations OR Less Developed World OR Lesser Developed Countries OR Lesser Developed Nations OR LMIC OR LMICS OR Low GDP OR Low GNP OR Low Gross Domestic OR Low Gross National OR Low-Income OR Lower GDP OR lower gross domestic OR Lower Income OR Middle-Income OR Poor Countries OR Poor Country OR Poor Economies OR Poor Economy OR Poor Nation OR Poor Nations OR Poor Population OR Poor Populations OR poor world OR Poorer Countries OR Poorer Economies OR Poorer Economy OR Poorer Nations OR Poorer Population OR Poorer Populations OR Third World OR Transitional Countries OR Transitional Country OR Transitional Economies OR Transitional Economy OR Under Developed Countries OR Under Developed Country OR under developed nations OR Under Developed World OR Under Served Population OR Under Served Populations OR Underdeveloped Countries OR Underdeveloped Country OR underdeveloped economies OR underdeveloped nations OR underdeveloped population OR Underdeveloped World OR Underserved Countries OR Underserved Nations OR Underserved Population OR Underserved Populations	
#6	#4 OR #5		1 164 208
#7	#3 AND #6		21 262
Intervention: Digital Health			
#8	MeSH terms:	"telemedicine"[MeSH]	
#9	Free text:	digital health or digital medicine or electronic health or ehealth) OR (mhealth or mobile health or mhealth or mobile app or mobile application or smartphone application or app or apps or reminder	
#10	#8 OR #9		538825
#11	#7 AND #10		376
Outcome: Treatment Adherence and Appointment Compliance			
#11	MeSH terms:	"Outcome Assessment (Health Care)"[Mesh]	
#12	Free text:	Treatment OR diagnosis OR adherence OR treatment adherence OR attendance OR compliance OR TB treatment adherence OR TB treatment compliance OR medication adherence OR doses OR cure OR completion OR default OR costs OR death OR lost to follow-up OR side effects OR adverse events OR mortality OR morbidity	
#13	#11 OR #12		18614555
#14	#11 AND #13		346

3.4 Study Selection

Search results from various databases were exported to Zotero reference manager. Duplicate studies were removed, and titles and abstracts were screened for eligibility independently by JLR and JF. Articles unrelated to TB or DH were excluded. Full text of the remaining articles was screened and analysed using Review Manager 5.4. We included randomized control trials and observational studies provided that the study included a control group, and reported an outcome relating to the treatment adherence or patient outcome.

Studies which did not exclusively relate to TB and DH were excluded. Additionally, we excluded studies where the study environment was not a LMIC. We did not include articles which only described study protocols, editorials, or positional papers.

3.5 Data Collection

Data extraction was completed by two researchers (JLR and JF). Conflicts were resolved through discussion. When no agreement could be reached, a third author intervened and mediated until a decision was reached. Information extraction from the included studies were:

1. Author(s)
2. Year of study
3. Country where study took place
4. Study environment
5. Study population
6. Nature of DH intervention
7. Study design
8. Outcomes assessed
9. Findings/results

Data was entered into Review Manager 5.4 by authors JLR and JF. A third researcher confirmed the entered data. The data extraction template is included in this document as **Appendix ii.**

3.6 Bias

Bias assessment was completed according to the guidelines stipulated by the International Cochrane Collaboration (Higgins et al., 2011). By conducting thorough bias assessment for each included study, we can report our associated risk of bias, accompanied by a summary of the reason(s) for bias. Two authors applied the criteria for bias assessment independently.

3.7 Synthesis of Results

Data analysis was conducted in accordance with guidelines set out by the Cochrane Handbook of Systemic Reviews for Interventions (Chandler et al., 2017). Data was analysed by the first author using Review Manager (RevMan) software based on the predetermined key criteria. A risk ratio (RR) and a corresponding 95% confidence interval (CI) was generated from each study assessed for dichotomous outcomes. Heterogeneity was assured by conducting the I-squared test.

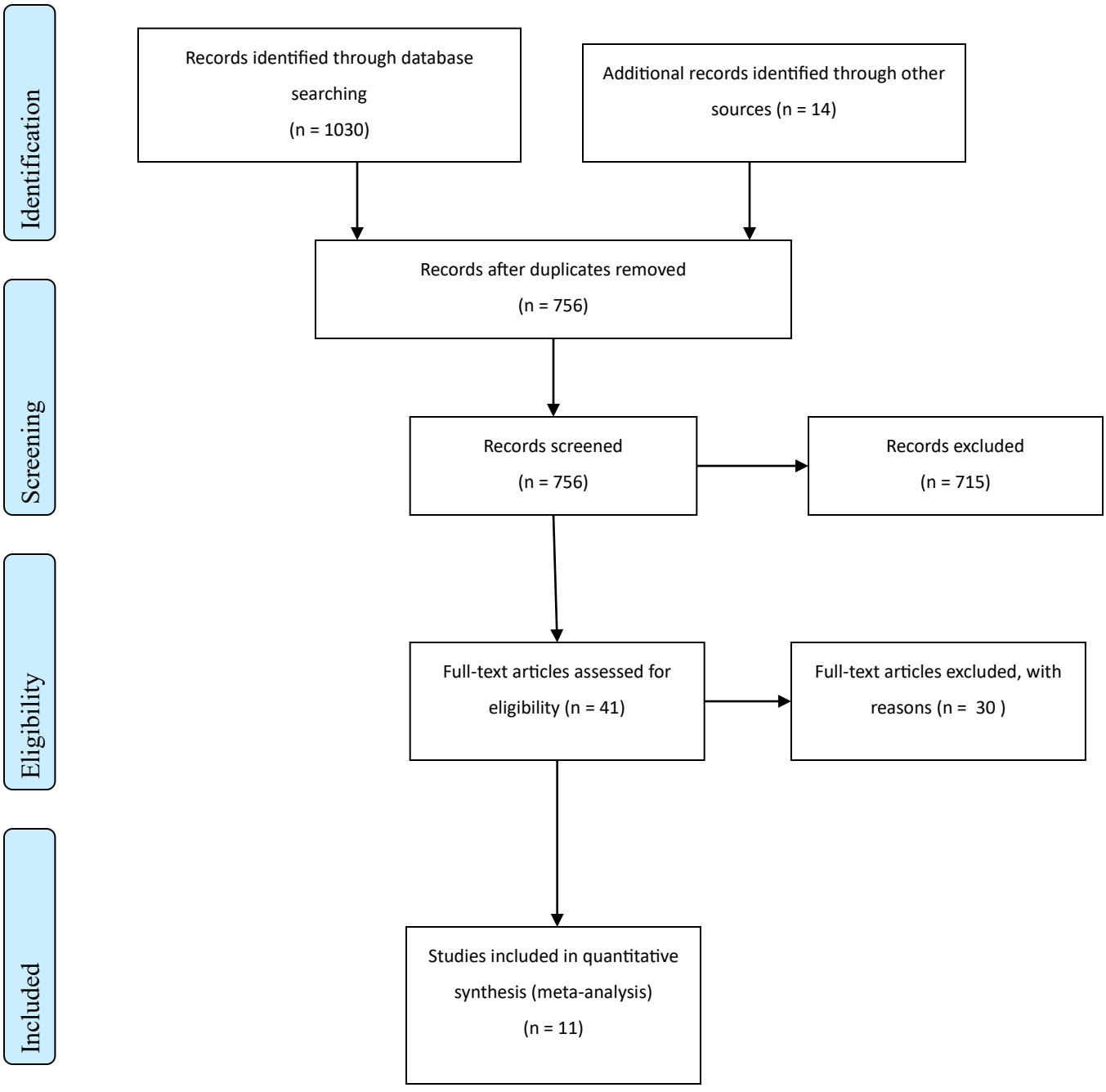
4. Results

4.1 Study Selection

A search of all the relevant databases initially yielded a total of 1030 articles. Grey literature sources yielded an additional 14 studies. Following the removal of 288 duplicates, the remaining articles were title and abstract screened, resulting in the removal of 715. Full text screening of 41 articles was undertaken. Eleven studies were included in the quantitative synthesis of this review.

A conclusive list of excluded articles and reasons can be found in Appendix iii. From the 30 articles which were excluded, four studies were conducted in in a non-LMIC environment. Three studies involved TB and HIV co-infected patients. Eight studies did not involve TB patients as the target population. Six studies reported outcomes which could did not align with patient outcome. Six studies were excluded on the basis of publication type (systematic review and meta-analyses). Four studies did not contain a control or comparison group.

PRISMA 2009 Flow Diagram



4.2 Included Studies Overview

Out of the eleven studies included in this review seven were RCTs (Bediang et al., 2018; Fang et al., 2017; Farooqi et al., 2017; I. & Juni, 2019; Kunawararak et al., 2011; Mohammed et al., 2016; Yoeli et al., 2019). Two studies were cluster randomized trials (CRTs) (Khachadourian et al., 2020; Liu et al., 2015). One study utilized a single arm with retrospective data (Broomhead & Mars, 2011). One study utilized a retrospective cohort (Guo et al., 2020). Table 3 presents all included study characteristics.

Three studies were conducted in China (Fang et al., 2017; Guo et al., 2020; Liu et al., 2015), two in Pakistan (Farooqi et al., 2017; Mohammed et al., 2016), one in South Africa (Broomhead & Mars, 2011), one in Kenya (Yoeli et al., 2019), one in Armenia (Khachadourian et al., 2020), one in Thailand (Kunawararak et al., 2011), one in Malaysia (I. & Juni, 2019), and one in Cameroon (Bediang et al., 2018).

Seven of the included studies implemented text message reminders as health interventions. One study implemented a combination of text messages and phone calls as reminders. Two studies implemented MM devices. One study implemented only phone call reminders. One study implemented VOT.

Table 3 Included study Characteristics

Author (year)	Study design, Country, Device	Population	Sample size	Nature of DH Intervention	Control	Reported outcomes
Guo et al, 2020	Retrospective Cohort China Smartphone	Patients with drug sensitive PTB	393 (158 control; 235 intervention)	Video Observed Therapy (VOT)	DOT	Fraction of doses observed Control group: 26/158 (16.4%) VOT group: 186/235 (79.1%) Higher number of doses observed among intervention group Fewer treatment discontinuations among VOT group
Fang et al, 2016	RCT China Mobile phone	PTB patients	350 (190 control; 160 intervention)	SMS reminders daily for 6 months	DOT	Treatment completion SMS group: 96.25% Control group: 86.84% Treatment completion rate significantly higher in SMS group (p 0.002)
Lui et al, 2015	Cluster Randomized Trial China Mobile phone and EMM	New PTB patients	4173 (1104 control; 1008 SMS; 997 MM; 1064 Combined)	SMS reminders Electronic medication packaging devices	DOT	The cluster geometric mean of the percentage of patient-months on TB treatment where at least 20% of doses were missed: Control: 29.9% SMS: 27.3% MM: 17.0%

I and Juni, 2018	RCT Malaysia Smartphone	Newly diagnosed PTB patients	93 (43 control, 50 intervention)	Whatsapp Health Education Module	Routine care	Treatment adherence Control group: 69.1% Intervention group: 81.8% No significance p 0.121 Treatment success Control group: 70.9% Intervention: 85.5% No significant p 0.121
Khachadourian et al, 2020	Stratified cluster RCT Armenia Mobile phone	Drug susceptible PTB patients in continuation treatment phase	385 (198 control, 187 intervention)	Daily SMS reminder and phone calls	DOT	Treatment success Control group: 184 (92.9%) Intervention group: 172 (92.0%) No statistically meaningful difference
Mohammed et al, 2016	RCT Pakistan Mobile phone	Newly diagnosed PTB patients with smear or bacteriologically positive Participants ≥15	2207	SMS reminder requiring response from patient	Routine care DOT	Treatment success SMS group: 719 (83%) Control group: 903 (83%) No significant difference
Bedliang et al, 2018	RCT Cameroon Mobile phone	Newly diagnosed PTB patients >18 years	279 (142 control; 137 intervention)	SMS reminder daily	Routine care	Treatment success at 5 months Control group: 75% Intervention group: 81% p=0.203 Patients cured at 6 months No effect

Broomhead and Mars, 2011	Single arm with retrospective data South Africa EMM	Newly diagnosed smear positive PTB patients	120 participants (96 control, 24 intervention)	Medication monitor	Routine care	Smear conversion at month 2 Control: 38.4% Intervention: 62.5% Cure rate Control: 32.3% Intervention: 75%
Farooqi et al, 2018	RCT Pakistan Mobile phone	TB patients	148	SMS reminder	Routine care	Treatment default Control: 4 SMS: 3 P=0.983 No statistical significance Treatment completion Control: 49 SMS: 49 No statistical significance
Kunawararak et al, 2011	RCT Thailand Mobile phone	Newly diagnosed smear positive PTB patients Age >15	98 (60 Non MDR; 38 MDR)	Phone call reminder daily	DOT	Treatment Success MDR Control: 14/19 Intervention: 19/19 p=0.0001 Non MDR Control: 29/30 Intervention: 30/30
Yoeli et al, 2019	RCT Kenya Mobile phone	Drug susceptible cliniocally diagnosed patients with at least 2 months treatment remaining	1104 (535 control; 569 intervention)	Text message requiring patient response	Routine care	Unsuccessful treatment outcome Control group: 70 (13.1%) Intervention group: 24 (4.2%) P<0.001 Treatment completed Control: 254 (47.48%) SMS: 285 (50.09%)

4.3 Study Characteristics

4.3.1 Participants

The total number of TB patients included in the eleven studies were 9350. All studies included both male and female participants, of varying ethnicity. All studies only included patients ≥ 15 years of age. A comprehensive table outlining sample sizes and study characteristics is represented in Table 4.

4.3.2 Nature of DH Interventions and Reported Outcomes

Text Message Reminder

Out of the seven studies which implemented text message reminders, two studies reported improved patient treatment adherence (Fang et al., 2017; Yoeli et al., 2019). The remaining five studies (Bediang et al., 2018; Farooqi et al., 2017; I. & Juni, 2019; Liu et al., 2015; Mohammed et al., 2016) reported that the text message reminder had no statistically significant impact on patients' outcomes.

Text Message and Phone Call Reminder

The one study which combined SMS reminders with phone calls reported no statistically meaningful difference on treatment success (Bediang et al., 2018).

Electronic Medication Monitor

One study which assessed both MM and SMS intervention on patience treatment adherence reported an improved adherence with patients who utilized a MM (Liu et al., 2015). A second study by (Broomhead & Mars, 2011) showed improved smear conversion and cure rate in patients utilizing a MM.

Phone Call Reminder

One study utilized only a phone call reminder and showed improved adherence (Kunawararak et al., 2011).

VOT

One study (Guo et al., 2020) assessed VOT as an alternative to DOT and reported a higher number of doses observed among the VOT group, as well as fewer treatment discontinuations among the VOT group.

Table 4: Results reported on by studies with their associated sample sizes and effect measures

Study ID	Outcome	Results		Effect Measure RR[95% CI]
(Fang et al., 2017)	**Completed treatment**	**SMS Group** 154/160 (96.25%)	**Control (DOT)** 165/190 (86.84%)	1.11 [1.04, 1.18]
(Guo et al., 2020)	**Fraction of doses observed ≥85%** **Treatment discontinuations ≥3 days** **Patient cured (smear negative) (after 3 months)**	**VOT Group** 186/235 (79.1%) 5 (2.2%) 38/40 (95%)	**Control (DOT)** 26/158 (16.4%) 11 (6.9%) 28/33 (84.85%)	1.12 [0.95, 1.31]
(Liu et al., 2015)	**Treatment success**	**SMS** 913/966 (96.1%) **MM** 887/955 (92.88%) **SMS and MM** 893/992 (90.02%)	**Control** 945/1066 (91.4%) 945/1066 (91.4%) 945/1066 (91.4%)	1.07 [1.04, 1.09] 1.05 [1.02, 1.08] 1.02 [0.99, 1.05]
(I. & Juni, 2019)	**Treatment adherence** **Treatment success**	**Intervention Group** 81.8% 47/55 (85.5%)	**Control** 69.1% 39/55 (70.9%)	1.21 [0.99, 1.47]
(Khachadourian et al., 2015)	**Treatment success**	**Intervention Group** 172/187 (92%)	**Control** 184/198 (92.9)	0.99 [0.93, 1.05]
(Mohammed et al., 2016)	**Treatment success**	**SMS** 917/1104 (83%)	**Control** 903/1093 (83%)	1.01 [0.97, 1.04]
(Bediang et al., 2018)	**Treatment success (at 5 months)** **Patients cured**	**SMS** 111/137 (81%) 87/137 (63.5%)	**Control** 106/142 (74.6%) 88/142 (62%)	1.09 [0.96, 1.23]
(Broomhead & Mars, 2011)	**Smear conversion rate (after 2 months)** **Cure rate (neg smear in last treatment month**	**MM** 15/24 (62.5%)15 18/24 (75%)	**Control** 37/96 (38.4%) 31/96 (32.3%)	2.32 [1.60, 3.36]
(Farooqi et al., 2017)	**Treatment success**	**SMS** 70/74 (94.6%)	**Control** 69/74 (93.2%)	1.01 [0.93, 1.10]
(Kunawararak et al., 2011)	**Treatment success**	**SMS** 30/30 (100%)	**Control** 29/30 (96.7%)	1.03 [0.94, 1.13]
(Yoeli et al., 2019)	**Treatment success**	**SMS** 545/569 (95.78%)	**Control** 465/535 (87.92%)	1.10 [1.06, 1.14]

4.4 Risk of Bias

To determine the quality of the included studies, the risk of bias was assessed. Figure 2 represents a risk of bias graph, whereas Figure 3 is a risk of bias summary across all studies.

Seven studies effectively randomized participants. Of the remaining four studies, two did not report on the randomization technique employed. Two studies did not claim randomization, given the nature of their study design (not RCTs).

Most studies did not report any allocation concealment. Given the nature of the DH interventions, the blinding of participant and personnel was either limited or not possible. Detection bias was not reported on by most of the studies. Nine of the studies had a low risk of attrition. Selective reporting was limited in the studies. Six studies had accessible study protocols. These protocols were assessed, and outcomes were compared to those reported on.

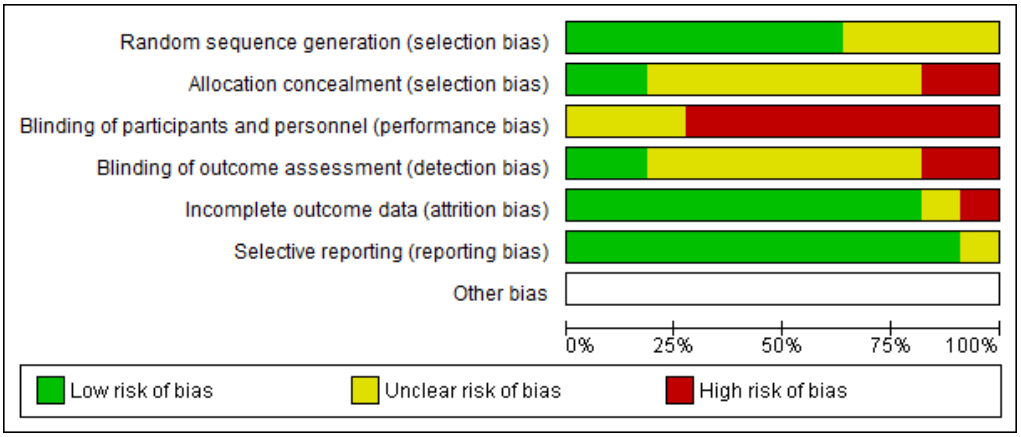


Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

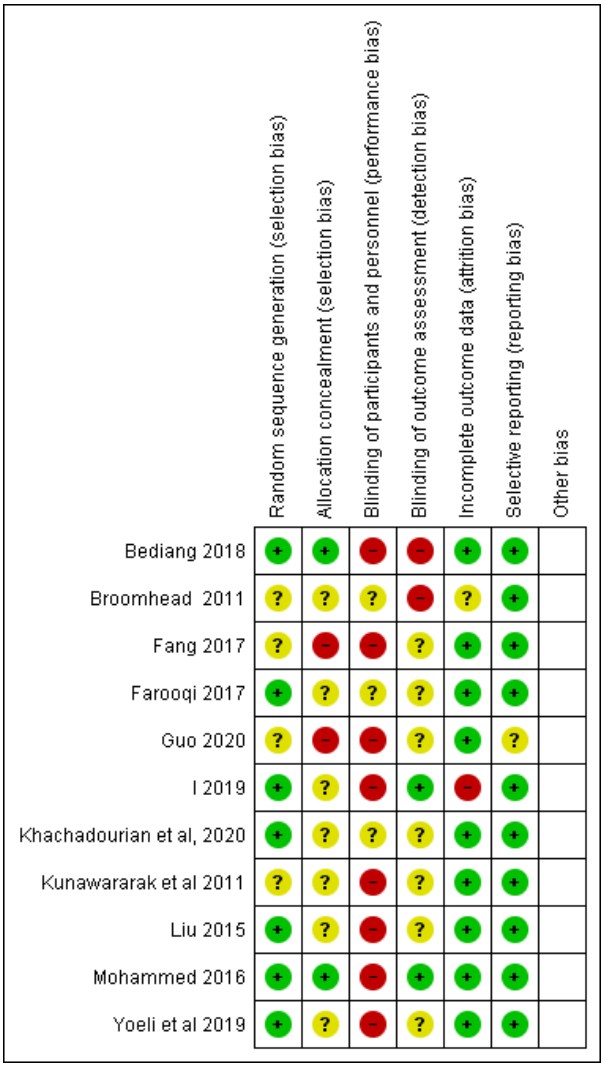


Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

4.5 Synthesis of Results

4.5.1 Text Reminders and Treatment Success

Six of the studies which employed text message reminders also reported treatment success. A fixed effect model comparing treatment success in patients who received text message reminders to those who did not get reminders are outlined in Figure 4. Out of all of the study participants 2603/2905 (89.60%) in the control text reminder group and 2527/2965 (85.23%) in the control group achieved treatment success (RR 1.06, 95% CI 1.02 to 1.10). .

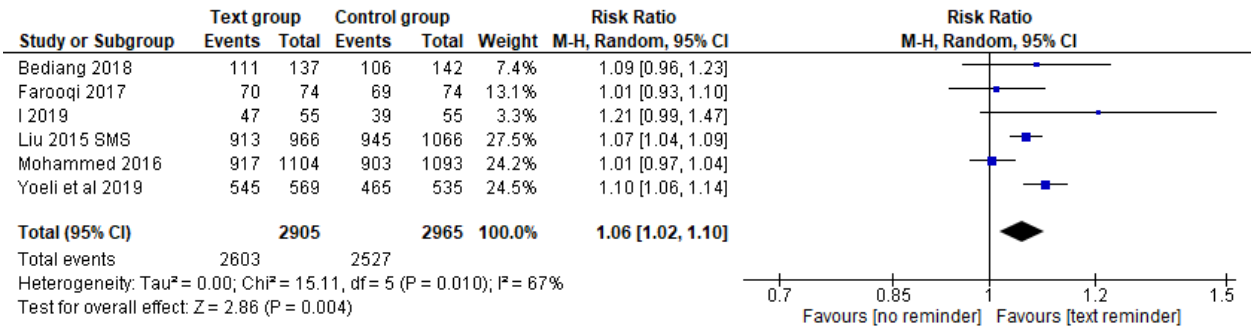


Figure 4 Forest plot showing the difference in treatment success between patient who received text reminders compared to those who did not

4.5.2 Electronic Medication Monitors and Treatment Success

Only two studies employed electronic medication monitors as DH interventions (Broomhead & Mars, 2011; Liu et al., 2015). One study (Broomhead & Mars, 2011) reported a moderate improvement in treatment success among the intervention group while another study found no significant improvement (Liu et al., 2015) RR 1.53 (95% CI 0.69 to 3.38).

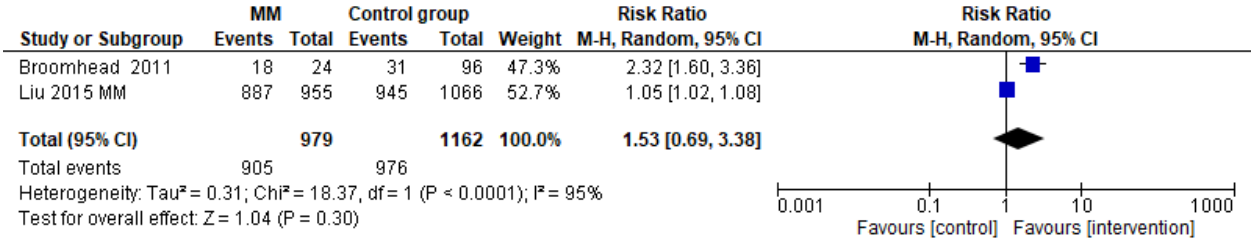


Figure 5 Forest plot showing the difference in treatment success between patients using an electronic medication monitor compared to the control group

4.5.3 Subgroup Analysis of One-Way vs Two-Way Text Reminders

A subgroup analysis of one-way reminders compared to interactive reminders shows a marginal difference in positive treatment outcome (One way RR 1.08 (95% CI 1.00 to 1.18) vs Interactive RR 1.05 (95% CI 1.01 to 1.09)).

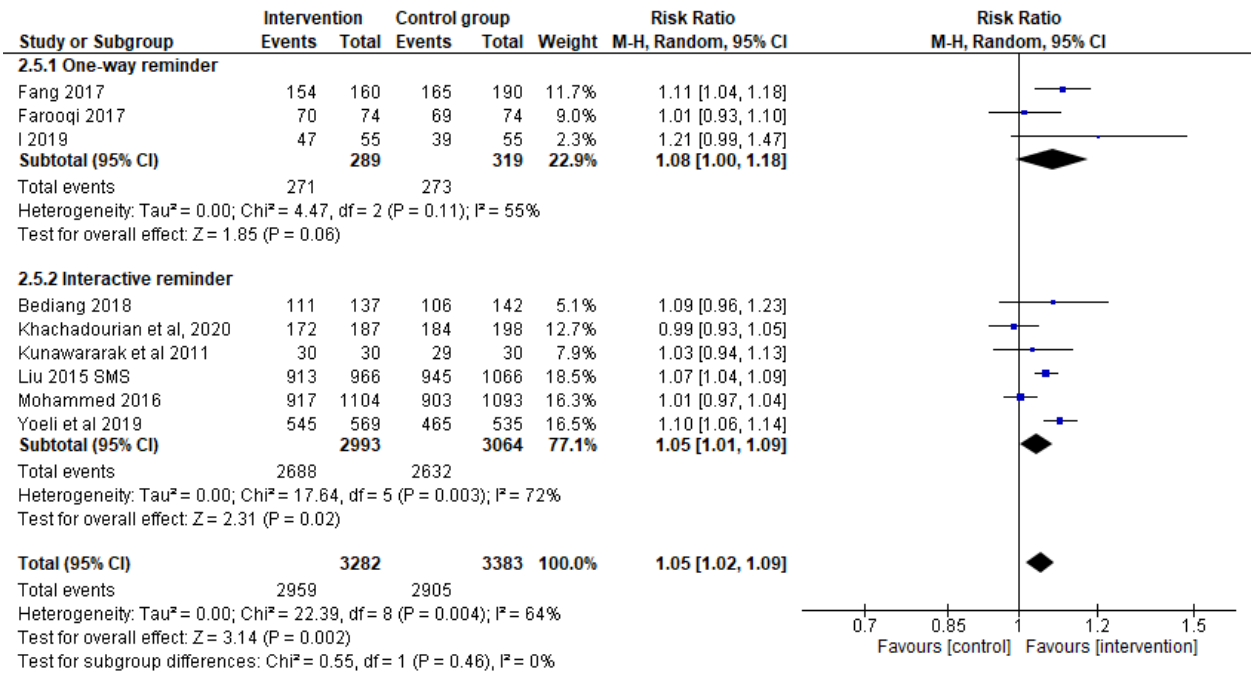


Figure 6: A subgroup analysis comparing the effect of one-way reminders to two way (interactive) reminders

4.6 Pooled Analysis of DH Solutions on Positive TB Patient Outcomes

The pooled analysis of all studies in Figure 7 indicates a marginal improvement in measures of positive patient outcomes RR 1.05 (95% CI 1.02 - 1.09).

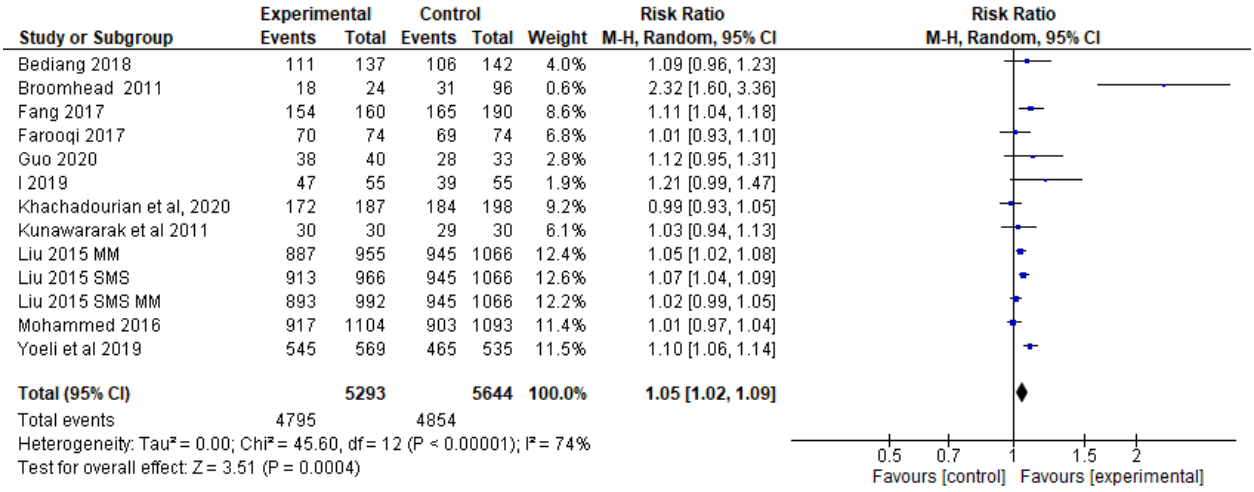


Figure 7 Pooled analysis of all studies to indicate overall effect of DH solutions on positive patient outcomes

5. Discussion

Even though 1030 articles were identified in our initial search, only eleven were included in this review. This is indicative of the fact that even through TB, DH, and the combination of both are often studied, scientifically robust trials in LMICs are limited. This could be attributed to a variety of factors: TB treatment is prolonged and often complicated. Resources and infrastructure required to implement DH solutions are often limited. For example, when implementing a text- based treatment reminder programme in a resource-strained setting, not all participants will have access to a personal cellular device with consistent connectivity. Furthermore, individuals who reside in rural areas could have difficulty with cellular signal, or the infrastructure required to charge their devices. This notion is echoed in a recent study by Saunders et al., (2018) which found that TB patients are likely poorer, more prone to food insecurity, and more likely to have an unsuccessful treatment outcome than the general public. This lack of access and infrastructure within LMICs, paired with the complexity of TB treatment and the monitoring thereof could add to the lack of robust studies assessing DH in TB patients in LMICs. In a recent review assessing mHealth solutions in LMICs and HICs assessed 210 studies and found 149 of those to be in HIC compared to only 61 in LMICs (AbazaHaitham & Marschollek, 2017).

The majority of the studies included in this review was conducted in Asia (8/11) which accounted for 7847 participants while the remaining studies were conducted in Africa (3/11) which accounted for 1503 out of the total 9350 participants. The study sample sizes varied in size. Southeast Asia is disproportionately represented in the included studies, which could highlight the limited spread and implementation of DH initiatives. This disparity could be attributed to the increased population density and globalization witnessed within this region as studies are likely to be conducted in areas where the fundamental infrastructure is functional and accessible by the population (Marcolino et al., 2018). Only studies by (Liu et al., 2015; Mohammed et al., 2016; Yoeli et al., 2019) consisted of sample sizes of more than 1000 participants. Even though drug-resistant TB is a serious concern in TB stabilization, only one study incorporated a drug-resistant arm in the conducted trial (Kunawararak et al., 2011).

Assessing the intervention modalities included in this study reveals that SMS text messages are most commonly employed and features in 70% of the included studies. The disproportional utilization of SMS text messages could be attributed to the simplicity, cost effectiveness, and

availability of cellular devices which offer SMS text functionality (Bobrow et al., 2016; R. Lester et al., 2019). Furthermore, SMS text messages require rudimentary infrastructure and is supported by all mobile networks. This is echoed by (AbazaHaitham & Marschollek, 2017) who compared mHealth solutions in HIC and LMICs and found that almost all mHealth solutions in HICs involve smartphone applications while most mHealth solutions in LMICs utilize SMS text messaging. The authors attributed this to availability and acceptability of SMS based solutions in LMICs. Although one-way SMS text messages which required no response from the patient are attributed to be less resource intensive, the unilateral mode of communication have often been criticized for lacking patient interaction. Two-way, or interactive reminder systems introduce privacy concerns and ethical considerations, with patients in past studies utilizing a similar modality often complaining about the intrusiveness of this system (DiStefano & Schmidt, 2016; Subbaraman et al., 2018). EMMs was implemented and assessed in two studies (Broomhead & Mars, 2011; Liu et al., 2015). These devices are costly and is more complex than regular SMS text message reminders and phone calls. Both included studies employing EMMs reported technical challenges and implementation difficulties, most notably battery failure on the devices, as well the potential for the patient to log a false reading when opening and closing the container without taking any medication. The combination of SMS reminders and EMMs was only assessed by (Liu et al., 2015), and reported no difference when compared to the other modalities or the control DOT group.

The outcome of this study was to assess the effect of DH solutions on TB patient treatment adherence in LMICs. Five studies a significant improvement in patient adherence (Broomhead & Mars, 2011; Fang et al., 2017; Guo et al., 2020; I. & Juni, 2019; Yoeli et al., 2019). The remaining studies six studies (Bediang et al., 2018; Farooqi et al., 2017; Khachadourian et al., 2015; Kunawararak et al., 2011; Liu et al., 2015; Mohammed et al., 2016) reported no statistically significant effect on treatment outcomes or patient adherence. The mixed nature of these results could be attributed to a range of factors. Firstly, studies varied in duration, nature of intervention, as well as outcomes measured. No two studies sent out the exact same text messages, meaning that the efficacy of the results could have been influenced by the content of the reminder rather than the reminder itself. The WHO (2017b) only recently established a comprehensive guide towards implementation of DH solutions for medication adherence. This guide outlines the process of

successful implementation of DH initiatives. This guide would likely serve to standardize DH intervention implementation and assessment, which should result in and increased methodological congruency for future studies. More than half of the studies included in this review was initiated before the publication of this guideline.

Overall, this review did not find significant superiority of DH interventions in TB patient adherence. A review by (Alipanah et al., 2018) focused on trials and observational studies, and noted that RCTs could, by design, affect the reported results due to lack of allocation and performance bias. By including observational studies in their assessment, they showed significant improvement of TB patient adherence with DH interventions.

Despite their best efforts, included studies still had various limitations. Firstly, even though the majority of studies involves RCT methodology, limited sample sizes affects the quality of the these studies. (Guo et al., 2020) employed a historical control group, which limits the effect of comparison. Secondly, the nature of these interventions complicates the processes of blinding during the execution of the study, which could result in potentially biased results. This notion is echoed by the risk of bias analysis included in this study (Figure 3) and also in other reviews assessing DH in TB care (Alipanah et al., 2018; Gashu et al., 2020). Two studies included in this review report limited assessment of baseline participant characteristics (Fang et al., 2017; Farooqi et al., 2017). Effective assessment of baseline patient characteristics could provide valuable insight into the socio-economic and environmental factors at play. Both studies which assessed the effectivity of EMMs noted technical difficulties with functionality and battery life (Broomhead & Mars, 2011; Liu et al., 2015).

This review has several limitations: This review focused on treatment outcome and success as a proxy for patient adherence. We did not review costs, implantation measures, or the qualitative experience of patients interacting with the DH solutions. The limited sample sizes and mixed methodological nature of the studies limits effective comparison.

Conclusions

The mixed results in this study could be attributed to unique factors within the various sub-populations assessed. DH solutions show promise in improving patient adherence and affecting

the TB patient care pathway, but these solutions should be tailored to best suit the population where they are implemented. Additional robust trials following standardized outcome measurements and implementation procedures like those outlines by the WHO (2017b) could provide valuable insight into the efficacy of DH interventions in LMICs.

Future studies should focus on a combination of DH intervention modalities, rather than the implementation of only one. A dynamic approach to DH implantation is likely to accommodate population specific aspects which could lead to more successful outcomes. Widespread studies investigating diverse environments and populations would contribute to assessing the efficacy of DH solutions affecting TB patient adherence in LMICs.

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Appendix i: Search Strategy

Population: Tuberculosis			
#1	MeSH terms:	"tuberculosis"[MeSH]	192 815
#2	Free text:	tb or tuberculosis or mycobacterium tuberculosis or mtb or Kochs disease OR Koch's Disease OR Koch Disease OR Multidrug resistant Tuberculosis OR MDR tb	301 499
#3	#1 OR #2		301 499
Population: LMIC			
#4	MeSH terms:	"developing countries"[MeSH]	75 306
#5	Free text:	Deprived Countries OR Deprived Population OR Deprived Populations OR Developing Countries OR Developing Country OR Developing Economies OR Developing Economy OR Developing Nation OR Developing Nations OR Developing Population OR Developing Populations OR Developing World OR LAMI Countries OR LAMI Country OR Less Developed Countries OR Less Developed Country OR Less Developed Economies OR Less Developed Nation OR Less Developed Nations OR Less Developed World OR Lesser Developed Countries OR Lesser Developed Nations OR LMIC OR LMICS OR Low GDP OR Low GNP OR Low Gross Domestic OR Low Gross National OR Low Income OR Lower GDP OR lower gross domestic OR Lower Income OR Middle Income OR Poor Countries OR Poor Country OR Poor Economies OR Poor Economy OR Poor Nation OR Poor Nations OR Poor Population OR Poor Populations OR poor world OR Poorer Countries OR Poorer Economies OR Poorer Economy OR Poorer Nations OR Poorer Population OR Poorer Populations OR Third World OR Transitional Countries OR Transitional Country OR Transitional Economies OR Transitional Economy OR	

		Under Developed Countries OR Under Developed Country OR under developed nations OR Under Developed World OR Under Served Population OR Under Served Populations OR Underdeveloped Countries OR Underdeveloped Country OR underdeveloped economies OR underdeveloped nations OR underdeveloped population OR Underdeveloped World OR Underserved Countries OR Underserved Nations OR Underserved Population OR Underserved Populations	
#6	#4 OR #5		1 164 208
#7	#3 AND #6		21 262
Intervention: Digital Health			
#8	MeSH terms:	"telemedicine"[MeSH]	
#9	Free text:	DH or digital medicine or electronic health or ehealth) OR (mhealth or mobile health or m-health or mobile app or mobile application or smartphone application or app or apps	
#10	#8 OR #9		538825
#11	#7 AND #10		376
Outcome: Cycle of Care Health Outcome			
#11	MeSH terms:	"Outcome Assessment (Health Care)"[Mesh]	
#12	Free text:	Treatment OR diagnosis OR adherence OR treatment adherence OR attendance OR compliance OR TB treatment adherence OR TB treatment compliance OR medication adherence OR doses OR cure OR completion OR default OR costs OR death OR lost to follow up OR side effects OR adverse events OR mortality OR morbidity	
#13	#11 OR #12		18614555

#14	#11 AND #13	346

EBSCOhost

Search ID	Search Terms	Results
S1	tb or tuberculosis or mycobacterium tuberculosis or mtb or Kochs disease OR Koch's Disease OR Koch Disease OR Multidrug resistant Tuberculosis OR MDR tb	774,908
S2	Deprived Countries OR Deprived Population OR Deprived Populations OR Developing Countries OR Developing Country OR Developing Economies OR Developing Economy OR Developing Nation OR Developing Nations OR Developing Population OR Developing Populations OR Developing World OR LAMI Countries OR LAMI Country OR Less Developed Countries OR Less Developed Country OR Less Developed Economies OR Less Developed Nation OR Less Developed Nations OR Less Developed World OR Lesser Developed Countries OR Lesser Developed Nations OR LMIC OR LMICS OR Low GDP OR Low GNP OR Low Gross Domestic OR Low Gross National OR Low Income OR Lower GDP OR lower gross domestic OR Lower Income OR Middle Income OR Poor Countries OR Poor Country OR Poor Economies OR Poor Economy OR Poor Nation OR Poor Nations OR Poor Population OR Poor Populations OR poor world OR Poorer Countries OR Poorer Economies OR Poorer Economy OR Poorer Nations OR Poorer Population OR Poorer Populations OR Third World OR Transitional Countries OR Transitional Country OR Transitional Economies OR Transitional Economy OR Under Developed Countries OR Under Developed Country OR under developed	1,538,304

	nations OR Under Developed World OR Under Served Population OR Under Served Populations OR Underdeveloped Countries OR Underdeveloped Country OR underdeveloped economies OR underdeveloped nations OR underdeveloped population OR Underdeveloped World OR Underserved Countries OR Underserved Nations OR Underserved Population OR Underserved Populations	
S3	digital health or digital medicine or electronic health or ehealth mhealth or mobile health or m-health or mobile app or mobile application or smartphone application or app or apps	899,826
S4	Treatment OR diagnosis OR adherence OR treatment adherence OR attendance OR compliance OR TB treatment adherence OR TB treatment compliance OR medication adherence OR doses OR cure OR completion OR default OR costs OR death OR lost to follow up OR side effects OR adverse events OR mortality OR morbidity	33,763,048
S5	S1 AND S2 AND S3 AND S4	218

Scopus Search Strategy (Results 312)

(TITLE-ABS-KEY (tb or tuberculosis or "mycobacterium tuberculosis" or mtb or "Kochs disease" OR "Koch's Disease" OR "Koch Disease" OR "Multidrug resistant Tuberculosis" OR "MDR tb")) AND ("digital health" or "digital medicine" or "electronic health" or "ehealth mhealth" or "mobile health" or "m-health" or "mobile app" or "mobile application" or "smartphone application" or app or apps) AND (ALL ("Cell phones" OR "Cellular phones" OR "Digital health interventions" OR "e-counselling" OR Facebook OR eHealth

OR e-health OR iphone OR "Internet-based" OR Messaging OR mHealth OR m-Health OR "Mobile apps" OR "Mobile applications" OR "Mobile based" OR "mobile devices" OR "mobile health" OR "Mobile phone based" OR "Mobile phones" OR "Mobile technology" OR MMS OR "online chat" OR "online social network" OR podcasts OR "portable electronic applications" OR eHealth OR "electronic health" OR SMS OR Smartphones OR "smart phone" OR "social media" OR "telecommunication in medicine" OR telecare OR telehealth OR "telephone-based" OR telehealth OR Telemedicine OR "Text messaging" OR "Text messages")) AND (ALL ("Deprived Countries" OR "Deprived Population" OR "Deprived Populations" OR "Developing Countries" OR "Developing Country" OR "Developing Economies" OR "Developing Economy" OR "Developing Nation" OR "Developing Nations" OR "Developing Population" OR "Developing Populations" OR "Developing World" OR "LAMI Countries" OR "LAMI Country" OR "Less Developed Countries" OR "Less Developed Country" OR "Less Developed Economies" OR "Less Developed Nation" OR "Less Developed Nations" OR "Less Developed World" OR "Lesser Developed Countries" OR "Lesser Developed Nations" OR LMIC OR LMICS OR "Low GDP" OR "Low GNP" OR "Low Gross Domestic" OR "Low Gross National" OR "Low Income" OR "Lower GDP" OR "lower gross domestic" OR "Lower Income" OR "Middle Income" OR "Poor Countries" OR "Poor Country" OR "Poor Economies" OR "Poor Economy" OR "Poor Nation" OR "Poor Nations" OR "Poor Population" OR "Poor Populations" OR "poor world" OR "Poorer Countries" OR "Poorer Economies" OR "Poorer Economy" OR "Poorer Nations" OR "Poorer Population" OR "Poorer Populations" OR "Third World" OR "Transitional Countries" OR "Transitional Country" OR "Transitional Economies" OR "Transitional Economy" OR "Under Developed Countries" OR "Under Developed Country" OR "under developed nations" OR "Under Developed World" OR "Under Served Population" OR "Under Served Populations" OR "Underdeveloped Countries" OR "Underdeveloped Country" OR "underdeveloped economies" OR "underdeveloped nations" OR "underdeveloped population" OR "Underdeveloped World" OR "Underserved Countries" OR "Underserved Nations" OR "Underserved Population" OR "Underserved Populations"))

Web of Science Results attained: 154

TOPIC: (tb or tuberculosis or mycobacterium tuberculosis or mtb or Kochs disease OR Koch's Disease OR Koch Disease OR Multidrug resistant Tuberculosis OR MDR tb) *AND* **TOPIC:** (Deprived Countries OR Deprived Population OR Deprived Populations OR Developing Countries OR Developing Country OR Developing Economies OR Developing Economy OR Developing Nation OR Developing Nations OR Developing Population OR Developing Populations OR Developing World OR LAMI Countries OR LAMI Country OR Less Developed Countries OR Less Developed Country OR Less Developed Economies OR Less Developed Nation OR Less Developed Nations OR Less Developed World OR Lesser Developed Countries OR Lesser Developed Nations OR LMIC OR LMICS OR Low GDP OR Low GNP OR Low Gross Domestic OR Low Gross National OR Low Income OR Lower GDP OR lower gross domestic OR Lower Income OR Middle Income OR Poor Countries OR Poor Country OR Poor Economies OR Poor Economy OR Poor Nation OR Poor Nations OR Poor Population OR Poor Populations OR poor world OR Poorer Countries OR Poorer Economies OR Poorer Economy OR Poorer Nations OR Poorer Population OR Poorer Populations OR Third World OR Transitional Countries OR Transitional Country OR Transitional Economies OR Transitional Economy OR Under Developed Countries OR Under Developed Country OR under developed nations OR Under Developed World OR Under Served Population OR Under Served Populations OR Underdeveloped Countries OR Underdeveloped Country OR underdeveloped economies OR underdeveloped nations OR underdeveloped population OR Underdeveloped World OR Underserved Countries OR Underserved Nations OR Underserved Population OR Underserved Populations) *AND* **TOPIC:** (digital health or digital medicine or electronic health or ehealth or mhealth or mobile health or m-health or mobile app or mobile application or smartphone application or app or apps) *AND* **TOPIC:** (Treatment OR diagnosis OR adherence OR treatment adherence OR attendance OR compliance OR TB treatment adherence OR TB treatment compliance OR medication adherence OR doses OR cure OR completion OR default OR costs OR death OR lost to follow up OR side)

Appendix ii: Data Extraction Template

Study ID (Author(s), year)	
Country	
Study Design	
Study Duration	
Participants Inclusion/exclusion criteria applied by study	
Sample Size Control Intervention	
Digital Health Intervention SMS/VOT/Phonecall	
Outcome Reported outcome Results Significance	
Limitations	
Notes	

Appendix iii: Excluded with Reasons

Author	Title	Reason for exlusion
Bassett et al., 2016	Sizanani: A Randomized Trial of Health System Navigators to Improve Linkage to HIV and TB Care in South Africa.	HIV co-infected patients
Blaya et al, 2014	Reducing communication delays and improving quality of care with a tuberculosis laboratory information system in resource poor environments: a cluster randomized controlled trial.	Programmatic assessment which does not include patients (Laboratory system assessed)
Blaya et al., 2010	Electronic laboratory system reduces errors in National Tuberculosis Program: a cluster randomized controlled trial.	Programmatic assessment which does not include patients (Laboratory system assessed)
Browne et al., 2019	Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial.	Study not conducted in LMIC environment (USA)
Buchman and Cabello, 2017	A New Method to Directly Observe Tuberculosis Treatment: Skype Observed Therapy, a Patient-Centered Approach	Study not conducted in LMIC environment
Chaiyachati et al, 2013	A pilot study of an mHealth application for healthcare workers: poor uptake despite high reported acceptability at a rural South African community-based MDR-TB treatment program	Target population is healthcare workers and not TB patients
Choun et al., 2017	Using mobile phones to ensure that referred tuberculosis patients reach their treatment facilities: a call that makes a difference.	Descriptive study which not include a control
DeMaio et al., 2001	The Application of Telemedicine Technology to a Directly Observed Therapy Program for Tuberculosis: A Pilot Project	Study not conducted in LMIC environment
Doulla et al., 2020	Reducing delays to multidrug-resistant tuberculosis case detection through a revised routine surveillance system.	Outcomes reported does not align with this review (sample turnaround time)

Farley et al., 2019	Evaluation of miLINC to shorten time to treatment for rifampicin-resistant Mycobacterium tuberculosis.	Outcome reported does not align with this study (time to treatment initiation)
Garfein et al., 2015	Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study.	Study not conducted in LMIC environment
Ggita et al., 2020	Experiences and intentions of Ugandan household tuberculosis contacts receiving test results via text message: an exploratory study.	Qualitative methodology followed (interviews)
Hoffman et al., 2010	Mobile Direct Observation Treatment for Tuberculosis Patients: A Technical Feasibility Pilot Using Mobile Phones in Nairobi, Kenya	Feasibility study that does not contain a control arm
Hunchangsith et al., 2012	Cost-effectiveness of various tuberculosis control strategies in Thailand.	Outcomes reported does not align with this review (cost effectiveness analysis)
Kranzer et al, 2012	Feasibility, yield, and cost of active tuberculosis case finding linked to a mobile HIV service in Cape Town, South Africa: a cross-sectional study.	Study population is HIV co-infected
Kumboyono et al., 2017	Short message service as an alternative in the drug consumption evaluation of persons with tuberculosis in Malang, Indonesia.	Methodology followed unclear. No information on frequency or content of text messages
Maduskar et al, 2013	Detection of tuberculosis using digital chest radiography: automated reading vs. interpretation by clinical officers	Study does not assess treatment outcome
Mahmud, et al., 2010	A text message-based intervention to bridge the healthcare communication gap in the rural developing world.	Target population is healthcare workers and not TB patients
Moayedi-Nia et al., 2019	The mTST - An mHealth approach for training and quality assurance of tuberculin skin test administration and reading.	Feasibility study that does not contain a control arm
Nguyen et al, 2017	Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: A prospective cohort study	No study control

Reis-Santos et al., 2019	Tuberculosis in Brazil and cash transfer programs: A longitudinal database study of the effect of cash transfer on cure rates.	Study does involve patient adherence
Sumari-de Boer et al., 2016	Feasibility of Real Time Medication Monitoring Among HIV-Infected and TB Patients in a Resource-Limited Setting.	HIV co-infected patients
Tesfaye et al,. 2017	Modelling the patient and health system impacts of alternative xpert® MTB/RIF algorithms for the diagnosis of pulmonary tuberculosis in Addis Ababa, Ethiopia.	Study focuses on programmatic TB diagnostic improvement
Thekkur et al, 2019	Outcomes and implementation challenges of using daily treatment regimens with an innovative adherence support tool among HIV-infected tuberculosis patients in Karnataka, India: a mixed-methods study.	HIV co-infected patients
Wagstaff et al., 2019	SMS nudges as a tool to reduce tuberculosis treatment delay and pretreatment loss to follow-up. A randomized controlled trial.	Study focuses on TB treatment initiation
Iribarren et al., 2015	Qualitative evaluation of a text messaging intervention to support patients with active tuberculosis: implementation considerations	Outcomes reported does not align with this review
Nglazi et al., 2013	Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment:a systematic review	Excluded on basis of publication type: Systematic review
Gashu et al.,	Does phone messaging improves tuberculosis treatment success? A systematic review and meta-analysis	Excluded on basis of publication type: Systematic review