Telemedicine-assisted Directly Observed Therapy (DOTS) for Tuberculosis: An Evidence-based Case Report

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ABSTRACT

Background: *Tuberculosis is a high-burden infectious disease requiring long-term treatment. Compliance is the key to cure; however, directly observed therapy (DOTS) is not always feasible. Telemedicine use in DOTS offers improved accessibility; however, its effectiveness has not been established. We aimed to investigate the effectiveness of telemedicine-based DOTS on treatment compliance in patients with tuberculosis.* ***Methods:*** *Databases including MEDLINE, Scopus, EMBASE, PubMed, and Cochrane were searched for studies implementing telemedicine-based DOTS until November 2nd, 2023. Studies were appraised for validity, importance, and applicability using the Oxford Centre of Evidence-Based Medicine tool, and the outcomes were graded based on their levels of evidence (LOE).* ***Results:*** *Our search yielded six systematic reviews. Telemedicine-based DOTS yielded favourable effects in improving adherence (LOE: I), treatment completion (LOE: II-III), and cure rates (LOE: II-III). Other outcomes, in terms of bacteriological resolution (LOE: II) and mortality (LOE: IV), were estimated to be non-inferior to those of DOTS. In terms of the telemedicine mode, the VDOTS yielded the highest LOE in improving adherence (LOE: I), followed by short messaging services (LOE: III) and medication monitors (LOE: III), which yielded similar effects. Results for phone reminders were contradictory, with the highest evidence suggesting that it might be ineffective for treatment completion (LOE: I-III) but may increase the cure rate (LOE: III).* ***Conclusion:*** *Telemedicine-based DOTS may improve adherence, treatment completion, and cure rate, and is non-inferior in terms of bacteriological resolution and mortality. Telemedicine-based DOTS can be considered for implementation; however, further high-quality studies in limited-resource settings are needed to strengthen the evidence.*

Keywords: *Tuberculosis, telemedicine, directly observed therapy, medication adherence, compliance.*

INTRODUCTION

Tuberculosis (TB) is a highly infectious disease caused by the acid-fast bacillus *Mycobacterium tuberculosis*. Endemic to regions including Indonesia, in 2021, the Ministry of Health reported that the incidence rate of TB was 354/100,000,[1] which makes tackling tuberculosis a critical issue, especially since the goal of annihilating TB is difficult to achieve. Many factors play important roles, including patient compliance with treatment regimens, which determine cure rates. In a previous study, fully compliant patients with TB achieved an overall cure rate of 91.3%.[2]

Treatment regimens for TB include long-term medications, and as stated previously, compliance is key to cure since failure to consistently take medications can lead to resistance that further challenges therapy. However, weekly in-person directly observed

therapy (DOTS) is burdensome for some patients because of time management problems and inconveniences. Some patients find it difficult to find someone to assist them in DOTS or take time away from their responsibilities. One study found that one of the reasons for DOTS failure is non-compliance due to non-willingness and prioritising work over treatment.[3] Furthermore, in limited resource settings, the number of healthcare personnel may not be sufficient to aid DOTS in day-to-day care.

Telemedicine is an electronic approach to healthcare provision delivered remotely.[4] Its use in aiding DOTS offers a wide range of conveniences that in-person DOTS does not offer. It uses technological means such as video, instant messaging, and phone calls that can connect remote interactions between the healthcare personnel and the patients, promoting better clinical monitoring and medication adherence.[5] This offers more flexibility for the patients in terms of accountability, as they can do video conferencing or asynchronously record a video of themselves ingesting their medications according to their own time.[6] In areas of high-income and low-disease burden, telemedicine-based DOTS has proven its capability in treatment monitoring and adherence of TB patients; while in other countries such as Kenya, India, Mexico, and Vietnam, results have been promising as well.[6-11] Areas with limited health personnel can benefit greatly from the utilization of telemedicine-based DOTS, but further evidence is needed in order to push further the confidence in using and investing in telemedicine-based DOTS for wide implementation. Thus, this study aimed to investigate the effectiveness of telemedicine-based DOTS compared with conventional (in-person) DOTS or self-administered therapy.

CLINICAL SCENARIO

A 40-year-old man presented to a primary healthcare facility with a history of bloody cough, night sweats, and enlarged neck lymph nodes. The patient smoked one pack of cigarettes per day and lived alone in a small, poorly-ventilated house with limited sunlight exposure. He works as a motorcycle taxi driver and mentioned that some of his passengers were coughing. Based on a positive acid-fast staining test, the patient was diagnosed with tuberculosis. However, when the treatment was administered, the patient found himself struggling to complete it because he did not have anyone to look after him, and the number of healthcare professionals in the nearby facility was very limited, which was overwhelming because of the high patient load. The facility is considering adopting telemedicine to help oversee the completion of treatment regimens.

CLINICAL QUESTION

How effective is telemedicine-based DOTS compared to conventional DOTS (in improving treatment compliance) in adults with confirmed TB?

METHODS

Literature search strategy and eligibility criteria

A literature search was performed in databases including PubMed, MEDLINE, Embase, Cochrane, and Scopus, which included grey literature. Studies implementing video-assisted DOTS were searched using the keywords listed in **Table 1** until 2 November 2023. The following inclusion criteria were implemented: (1) study design, systematic review of clinical trials, and clinical trials; (2) population, adults with confirmed tuberculosis; (3) intervention, telemedicine-assisted DOTS; (3) Outcome assessed, including adherence to treatment and other clinically relevant outcomes. In contrast, studies with inaccessible full texts, incomplete studies at the time of search, studies in languages other than English or Indonesian, and inappropriate study designs, such as pilot studies, commentaries, editorials, notes from the field, and studies without control groups, were excluded.

Data Extraction

Five independent authors extracted data from included studies using predetermined tabulations in Microsoft® Word for Mac Version 16.78 (Microsoft Corporation, Redmond, WA, 2023). The following data were extracted: (1) author and publication year; (2) study design;

Table 1. Search keywords in databases.

Database	Keywords	Hits
PubMed	("Tuberculosis"[Mesh]) AND (("Telemedicine"[Mesh] OR Video[Title/Abstract] OR electronic[Title/Abstract]) AND ("Directly Observed Therapy"[Mesh])) AND ("Treatment Adherence and Compliance"[Mesh] OR ("Compliance"[Mesh]) OR Adherence[Title/Abstract])	65
Cochrane	#1 MeSH descriptor: [Tuberculosis] explode all trees #2 MeSH descriptor: [Telemedicine] explode all trees #3 electronic #4 video #5 MeSH descriptor: [Directly Observed Therapy] explode all trees #6 MeSH descriptor: [Compliance] explode all trees #7 MeSH descriptor: [Medication Adherence] explode all trees #8 Adherence #9 #2 OR #3 OR #4 #10 #5 AND #9 #11 #11 #6 OR #7 OR #8 #12 #12 #1 AND #10 AND #11	9
Scopus	TITLE-ABS-KEY(Tuberculosis AND ((telemedicine OR video OR electronic) AND (Directly Observed Therapy)) AND (adherence OR compliance))	81
EMBASE	12 1 and 10 and 11 11 6 or 7 or 8 10 5 and 9 9 2 or 3 or 4 8 Adherence.mp. 7 Compliance.mp. 6 (Treatment Adherence and Compliance).mp [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 5 directly observed therapy/ 4 electronic.mp. 3 video.mp.[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 2 telemedicine/ 1 tuberculosis/	54
MEDLINE	1. Tuberculosis.mp. 2. Telemedicine.mp. 3. Video.mp. 4. Electronic.mp. 5. Directly Observed Therapy.mp. 6. Adherence.mp. 7. Compliance.mp. 8. 6 or 7 9. 2 or 3 or 4 10.1 and 9 11.5 and 10 12.8 and 11	84

(3) characteristics of included studies, including number, participants, and interventions; and (4) outcomes and level of evidence (LOE).

Critical Appraisal

Critical appraisal encompassing validity, importance, and applicability was performed using the Oxford Center for Evidence-Based Medicine (OCEBM) critical appraisal tool for systematic reviews.[12] Pooled effects were analysed by studies, absolute risk reduction/increase (ARR/I) and number needed to treat/harm (NNT/H) were algebraically calculated to assess the importance, referring to 27.2% as the patient expected event rate (PEER) as reported by Lolong et al's study in Indonesia.[13] Furthermore, ranking was done based on LOE as guided by OCEBM.[14] These were performed by the five reviewers and one reviewer independently evaluated the appraisal. Any disagreements were

resolved by consensus.

Detailed appraisal was summarized in a predetermined tabular form. LOE was graded as follows:

a. LOE assessment started with level I for systematic reviews and/or meta-analyses, level II for randomized controlled trials (RCTs), and level III for non-randomized cohort/follow-up studies.
b. LOE was upgraded by one for large pooled effect (mean difference [MD]>±5, risk ratio [RR]>2.5 or RR<0.40, odds ratio [OR] >2.5 or OR<0.40)
c. LOE was upgraded by two for very large pooled effect (MD>±10, RR>5 or RR<0.25, OR>5 or OR<0.25).
d. LOE was downgraded by one each for (i) imprecision (wide confidence intervals [CI]: upper limit – lower limit >±10), (ii) indirectness (inappropriate study population, intervention, comparison, or outcomes [PICO]), or (iii) poor internal validity (validity score <5).
e. LOE was downgraded by two points each due to very serious (i) imprecision (very wide CI: upper limit – lower limit of 95% CI >±20) or (ii) very poor study quality (validity score <4).

RESULTS

Study Selection

Overall, 293 studies were obtained from several databases and filtered based on the inclusion criteria. After removing duplicates, 59 full-text articles were screened. Research papers that did not fulfil the inclusion criteria were excluded, yielding a total of six systematic reviews and 10 original articles. Finally, six studies were included in this review. A flowchart of the literature search process is shown in **Figure 1**.

Characteristics of Included Studies

The six included studies were systematic reviews, of which two pooled the results using statistical analysis. One study specifically focused on patients with latent TB, one investigated only patients with active TB, and the remaining four included all patients with TB. The types of telemedicine interventions analysed included synchronous and asynchronous video-assisted DOTS (VDOTS) in one study, mobile phone short message service (SMS) in another study, and a combination of the aforementioned means in addition to phone calls, reminders, or medication monitoring in the rest of the studies. In synchronous VDOTS, the patients were required to engage in video calls at predetermined schedules using Facetime, Zoom meetings, or other applications while taking their medications up until treatment completion.[15] Meanwhile, asynchronous VDOTS allowed the patients to record themselves while taking the medications and submitting these videos at regular intervals, such as weekly.[15] SMS interventions were in the form of messages delivered to the patients' phones as daily reminders, after which the patients can reply to the message confirming that they have taken the drug.[16,17] The same principle was used for calls to the patients' personal phones, by which the patients were reminded to take the drug.[15] Medication monitors were in the form of a digital pillbox, which automatically sent messages to the server each time the patient opened the box, indicating that the patient had taken the drug.[18] Three studies used conventional DOTS as a comparator, one compared the intervention effects with self-administered therapy, and the remaining two included a combination of both as a control group. Detailed characteristics of the included studies are shown in **Table 2**.

Validity

All six studies that were included in this review had acceptable validity, although some components were not fulfilled. All included studies critically appraised their papers, addressed a focused question, and had clear inclusion and exclusion criteria for select studies. However, most articles did not include only high-quality studies and only two out of six studies assessed heterogeneity. These are shown in **Table 3.**

Importance

Results regarding importance and applicability are shown in **Table 4**. Truong et al.[15] reviewed nine studies, including three RCTs

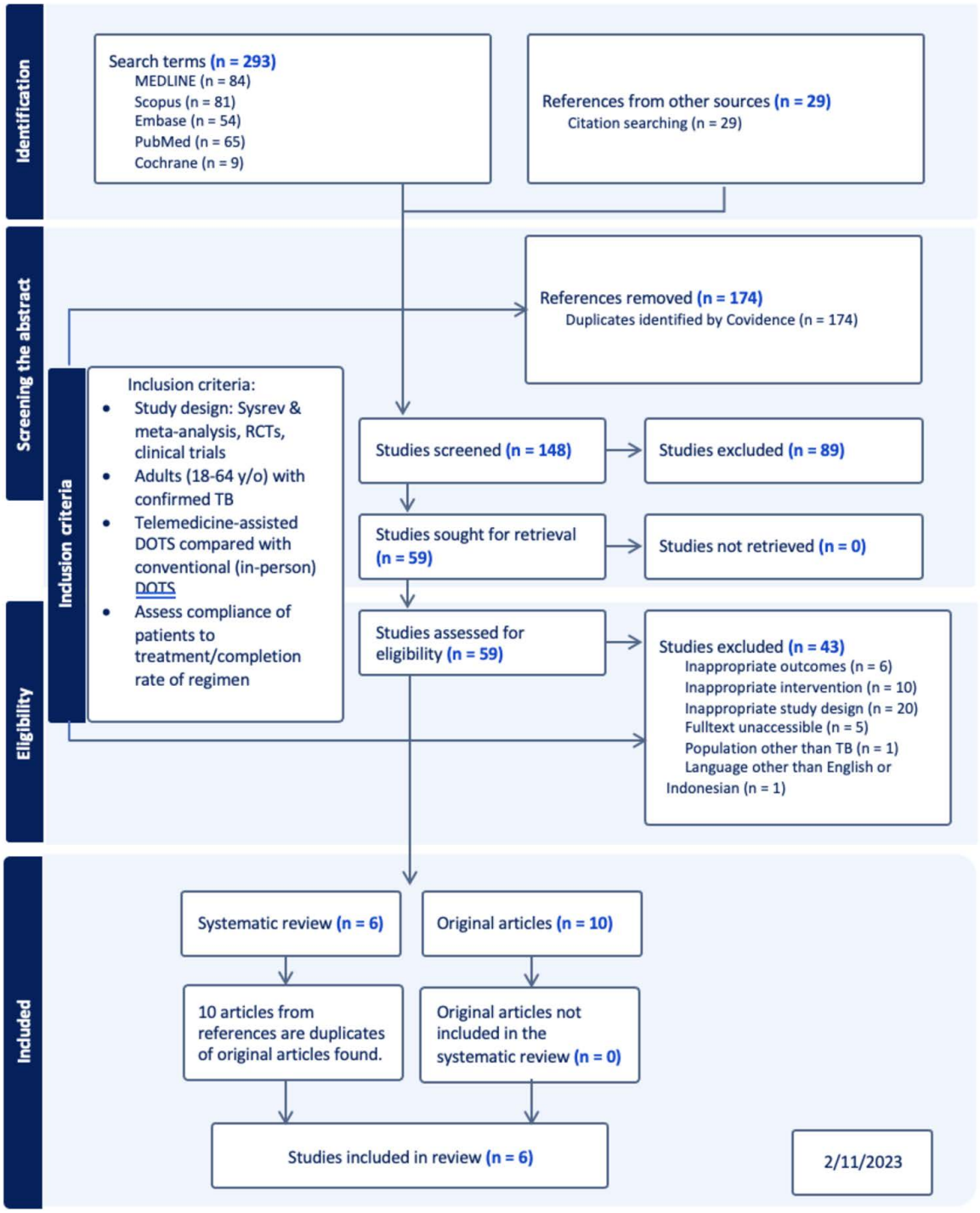

Figure 1. Flowchart of Literature Search and Selection

and six nonrandomised studies. The evaluated outcomes included medication adherence, treatment completion, and bacteriological resolution. Medical adherence was likely to be 2.79 times higher in subjects who underwent VDOTS than in those who underwent DOTS (LOE: I). Treatment completion was 1.33 times higher in the VDOTS group; however, statistical significance was not reached during the meta-analysis (pooled RR=1.33 [95%CI=0.73, 2.43], LOE: II). Bacteriological resolution had similar outcomes (pooled RR=1.06 [95%CI=1.01–1.11]) in groups with either asynchronous/synchronous VDOTS or control (DOTS) (LOE:

II). The pooled RR had narrow confidence intervals, which strengthened our results. In this review, a notable reduction in LOE was observed due to the inclusion of a study with a high risk of bias. Considerable heterogeneity was also observed in the proportion of observed doses (I2=96%).

Wong et al.[16] included 14 studies, including 2 RCTs, 2 controlled trials, 1 mixed method, and 9 nonrandomised studies. The results for the effects of VDOTS were reported to be similar but had a lower LOE, as they did not perform a statistical analysis (LOE: III). Low-quality studies were also included. Portions of the reported relative risk ranges did not reach statistical significance, except for phone reminders versus self-administered treatment, which yielded better outcomes (LOE: III).

Alipannah et al.[17] reviewed 2 RCTs in which the experimental group received phone call reminders or SMS. The results on treatment completion were all similar and statistically insignificant (LOE: I-II). The only exception was 1 RCT that compares SMS and DOTS (Risk ratio [RR]=1.11 [95%CI:1.04–1.18]), but neither group had a sizeable advantage over the other (LOE: II). The review did not find any differences in cure rates (LOE: II). The ARI was calculated to be 6%, and the NNT was 16.7. Alipannah et al. also reviewed one cohort study analysing the cure rate of phone reminders, for which a better outcome was obtained, but without significance (LOE: II). The mortality rate of VDOTS in one cohort study showed no significant difference; however, low precision was achieved with broad confidence intervals, and the quality of the study was poor (LOE: IV). Another cohort study and two RCTS were reviewed, showing no difference in those receiving phone reminders (LOE: II).

Ngwatu et al.[18] reviewed seven studies (three observational studies and four RCTs) that compared telemedicine (medication on monitors, SMS, and VDOTS) with controls (DOTS or self-administered therapy). The cure rate was better in the monitoring group than in the control group (LOE: III). A comparison of cure rates was not performed using VDOTS. Similar to Wong et al., data regarding treatment completion were inconclusive, as they did not implement statistical analyses or provide information that would explain heterogeneity. Results were given in ranges (RR=0.99 [95%CI:0.93–1.05] to RR=1.47 [95%CI:0.96–2.25]), with neither spectrum showing a clinically important effect (LOE: III).

Ridho et al.[19] reviewed 16 RCTs comparing the interventional (direct and indirect VDOTS, response to SMS and phone calls, and pill counting through a monitor box) and control (DOTS) groups. Subjects who underwent VDOTS expressed a higher likelihood of treatment completion than the controls (LOE: III). In contrast, treatment adherence was similar (LOEIII), and the results were not statistically significant. The review also concluded that the cure rates between the phone call reminder and DOTS groups were similar (LOE: III). The cure rate between the SMS and control groups was contradictory (LOE: III), as two RCTs found no difference, but one RCT showed that the SMS group had a better cure rate, despite the lack of statistical significance and wide confidence intervals.

Nglazi et al.[20] also reviewed studies (s) on the cure rate of SMS versus DOTS in treating TB and found that it was similar between groups (LOE: III); however, no confidence interval was available. Telemedicine also had a higher completion rate (LOE: II) and treatment adherence (LOE: III). Nevertheless, the adherence results were not statistically significant.

Applicability

The included studies may not be applicable based on population characteristics, as the majority of the data obtained from the studies were from developed countries; hence, many factors such as quality, advancement of TB care, treatment regimens, and others may differ from the limited-resource setting. However, the interventions could be used and may yield similar results when conducted in this setting, considering that no adverse effects were reported; utilising telemedicine would provide more benefits than it may harm.

DISCUSSION

Telemedicine for Tuberculosis Therapy

Telemedicine is an electronic approach to healthcare provision that can overcome geographical barriers and has become a potential key player in recent years in our fight to end TB.[4] Indeed, the length and complexity of TB therapy pose great challenges to compliance, which is crucial to ensuring cure and preventing resistance.[21] Telemedicine provides a way to track and remind patients to be accountable to their regimen, even when no one else nearby is available. Based on telemedicine types, this report showed that out of other approaches, VDOTS had the highest LOE in increasing medication adherence and completion. The combination of audio and visual inputs required in VDOTS not only ensures that there is less chance for patients to fake their drug-taking account but also allows patient-centred care through possible interactions.[22] In contrast, SMS, which involves only text in words, might yield no difference in treatment completion, adherence, and cure rate (LOE: III). Notably, the results for phone reminders were contradictory, with the highest evidence suggesting that it was likely to be ineffective for treatment completion (LOE: I-III) but might increase the cure rate (LOE: III). These contradictory outcomes might arise because of the differences in the populations included, which comprised both latent and active TB patients. Patients with latent TB are likely to be treated with one or two drugs,[23] in contrast to those with active TB, who typically require at least four drugs. Thus, it may be easier for patients with latent TB to comply with the regimen, yielding no difference in comparison with traditional DOTS when combined. Medication monitoring may increase the cure rate (LOE: III).

Medication Adherence

Medication adherence is defined as an individual's behaviour to follow the recommended treatment from healthcare providers.[24] Adherence to treatment is important as poorer condition, which leads to high mortality and morbidity rates, can be seen in patients with poor adherence.[25] In this report, patients who underwent VDOTS presented better outcomes than DOTS. Despite similar outcomes for other telemedicine approaches, this result is important because telemedicine is more economical, cost-effective, and can eliminate distance barriers.[26]

Treatment Completion/Success

Treatment completion, or the successful conclusion of the full regimen in TB, is vital for a variety of reasons.[27] First, drug-resistant TB can develop. When the treatment is incomplete, some TB pathogens may survive, potentially causing more severe and resistant forms of the disease. Second, TB remains contagious in both untreated and partially treated patients. Third, it is a public health concern. Ensuring that all patients complete their treatment helps control the spread of the disease in communities and reduces the burden on the healthcare system. Fourth, for the patient's individual health, completing treatment is essential to prevent the disease from progressing, causing complications, or leading to more severe forms of TB.

Similar or inconclusive results of treatment completion in our report prove that telemedicine is more effective than DOTS. However, this is reassuring because of its non-inferiority and convenience. Small sample sizes were used in the original studies, which can limit the ability to detect significant differences.[28] A larger sample size might provide greater clarity. Similarly, the study design and methodology could impact the results.[28] In such cases, further research and examination of subgroups or additional factors may be necessary to better understand why there is no significant difference in treatment completion and to inform healthcare policies.

Cure Rate

The overall cure rate was better for telemedicine DOTS. This indicates that those who underwent telemedicine DOTS had a much larger proportion of bacteriological resolution. However, the validity scores for some studies reporting cure rates were low.[29,30] Therefore, these results should be interpreted with caution, as the evidence provided may not necessarily depict actual population estimates. However, the rate of bacteriological resolution remains a key indicator of TB.[31,32]

Other Reported Outcomes

Mortality has also been investigated; however, the results have been inconclusive. Indeed, mortality was reported to be similar aside from one study; however, this was not clinically important because of the low ARI, high NNT, and low precision. The results should be interpreted with caution because the studies were contradictory and heterogeneous. The proportion of doses observed was also reported to be higher in the VDOTS; however, this measure might be less important than compliance, which is more objective.[31]

Study Implications and Recommendations

Telemedicine-based DOTS may offer increased adherence with the additional benefit of allowing it to be performed over a distance without requiring the face-to-face presence of medical professionals. Therefore, telemedicine-based DOTS are suitable for applications in archipelagic states. However, in the application of telemedicine-based DOTS, accessibility remains an issue in remote areas where Internet access is not always available. Infrastructure development is crucial for enabling the VDOTS, which yields the highest LOE. Moreover, over half of the studies in this report were conducted in developed countries, such that evidence of benefits in resource-limited settings is yet to be discovered. Despite this, recent rapid technological development, actuated by the increasing number of Internet users over the last 5 years,[33] serves as a promise for a continual increase in access to telemedicine. Furthermore, despite the lower LOE, other telemedicine modalities, including SMS and phone calls, may be more accessible, even in rural areas. Further studies on the use of other telemedicine modalities, specifically in rural areas, should be conducted. Overall, there is great potential for telemedicine-based DOTS to be applied on a larger scale, and patient preferences should be considered when recommending telemedicine to TB patients.

Limitations

This study had some limitations. Some of the studies reviewed had a low LOE, as seen in the poor validity score, and only two used statistical analysis, such that the overall effect could not always be concluded quantitatively. Moreover, the population included a variety of patients with active, latent, and extrapulmonary TB, such that interpretation was limited by possible heterogeneity, which most studies did not address. Furthermore, the effectiveness of telemedicine in settings with limited resources remains unknown. Further meta-analyses of RCTs involving only patients with active TB, conducted in limited-resource settings, are warranted to substantiate this evidence.

CONCLUSION

In conclusion, telemedicine-based DOTS may be effective in improving adherence, treatment completion, and cure rate, as well as being non-inferior in terms of bacteriological resolution and mortality. In particular, VDOTS yielded the highest LOE compared to the other means of telemedicine. Telemedicine can be considered for implementation because it enables DOTS to be conducted remotely in areas where experts may be lacking. However, further high-quality studies involving only blinded RCTs on patients with active tuberculosis and those conducted in limited-resource settings are needed to strengthen this evidence.

LIST OF ABBREVIATIONS

ARR/I	Absolute risk reduction/increase
CI	Confidence intervals
DOTS	Directly observed therapy
LOE	Level of evidence
MD	Mean difference
NNT/H	Number needed to treat/harm
NA	Not applicable
NR	Not reported
OCEBM	Oxford Center for Evidence-Based Medicine
PEER	Patient expected event rate
RR	Risk ratio
SMS	Short messaging service
TB	Tuberculosis
VDOTS	Video-assisted directly observed therapy

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CONFLICT OF INTERESTS

The authors declare there is no conflict of interest.

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Table 2. Characteristics of included studies.

Author; Year	Study Design	Included studies					Main outcomes and LOE
		Number	Included study designs	Total participants	Population tuberculosis type	Interventions vs comparators	
Truong et al; 2021[15]	Systematic review and meta-analysis	9	3 RCT 1 uncontrolled pre-post intervention study 4 prospective cohorts 1 retrospective cohort	1,091 patients in VDOTS 1,390 in DOTS	Latent, active pulmonary, and extra-pulmonary tuberculosis	Asynchronous and synchronous VDOTS vs In-person DOTS	Compared to DOTS, patients with VDOTS were found to have: - higher medication adherence (LOE: I) - higher proportion of doses observed (LOE: II) - higher bacteriological resolution (LOE: II) - similar treatment completion (LOE: II)
Wong et al, 2022[16]	Systematic review	14	2 RCTs 2 Controlled trials 1 Mixed methods study 9 Non-randomized studies	4,264	Latent	Digital health interventions (SMS/phone reminders/ VDOTS) vs DOTS/ self-administered treatment	- Compared to DOTS/self-administered treatment, treatment completion with SMS reminders was similar (LOE: III) - Compared to self-administered treatment, treatment completion with phone reminders was better (LOE: III) - Compared to DOTS, treatment completion with phone reminders was similar (LOE: III) - Compared to DOTS, completion rate with VDOTS was better (LOE: III)
Alipanah et al; 2018[17]	Systematic Review and meta-analysis	9	6 RCT + 3 Cohort Studies	7649	Adults or children in any setting undergoing TB treatment Includes pulmonary, extrapulmonary, smear-positive or negative, and drug-susceptible and- resistant TB, and patients with HIV	Digital health interventions (video, phone, and SMS reminders): VOT vs DOTS SMS reminders vs DOTS Phone reminders vs DOTS	SMS reminders had a higher treatment completion rate compared to DOTS (LOE: II) VDOTS and DOTS in 2 CS were not significantly different in terms of treatment completion (LOE: II) and mortality (LOE: III)
Ngwatu et al; 2018[18]	Systematic review	7	3 observational & 4 RCT	7,005	Active TB	Medication monitors, SMS, vDOTS vs DOTS/Self-administered treatment	Medication monitor: improvement in smear conversion at 2 months & statistically significant effect on adherence relative to standard care (LOE: III) SMS studies showed no significant effect on clinical outcomes and adherence (LOE: III) VDOTS: effect on treatment completion rates was not statistically significant (LOE: III)

Ridho et al, 2022[19]	Systematic Review	16	16 RCTs	9789	15 y/o and above, TB all types	Medication adherence could be measured using self-report on the device directly (VDOTS) and indirectly (VOT), responding to phone calls and SMS text messages, detecting drug taking through a monitor box, or pill counting. Vs DOTS	Compared to DOTS, treatment completion was higher in: - VDOTS (LOE: II) - Ingestible sensors (LOE: III) Compared to DOTS, treatment completion was relatively less to similar in: - SMS (LOE: II) - Phone reminders (LOE: I) Compared to DOTS, treatment adherence was higher in: - VDOTS (LOE: II) - SMS (LOE: II) Compared to DOTS, the cure rate was higher in: - Phone call reminder (LOE: II) - SMS (LOE: II)
Nglazi et al; 2013[20]	Systematic Review	4	1 mixed-methods 1 retrospective cohort 2 pilot studies	565	Adults (including pregnant women) or children receiving TB treatment	Mobile phone text messages vs no intervention or other interventions for promoting adherence	- Higher completion rate was achieved with text messages (LOE: II) - Self-reported adherence, cure rate, and treatment success were similar (LOE: III)

VDOTS, video directly observed therapy; DOTS, directly observed therapy; RR, risk ratio; MD, mean difference; SMS, short messaging service; NR, not reported; LOE, level of evidence.

Table 3. Validity of Included Studies.

Author; Year	Validity					
	Q: *Does the systematic review address a focused question (PICO) and use it to direct the search and select articles for inclusion?*	**F,** *searched to find all the relevant evidence?*	**Have** *the studies been critically appraised?*	**Did** *they only include high-quality studies?*	**T,** *have the results been totaled up with appropriate summary tables and plots?*	**H** *has heterogeneity between studies assessed and explained.*
Truong et al; 2021[15]	✓	?	✓	✗	✓	✓
Wong et al, 2022[16]	✓	✓	✓	✗	?	✗
Alipanah et al; 2018[17]	✓	✓	✓	✗	✓	?
Ngwatu; 2018[18]	✓	✓	✓	✗	?	✗
Ridho; 2022[19]	✓	✓	✓	✗	?	✗
Nglazi et al; 2013[20]	✓	✓	✓	✗	?	✗

✓, no serious limitation; ✗, serious limitation; ?, unclear/some concerns.

Table 4. Importance and applicability of the results in each included study.

Author; Year	Importance			Applicability			LOE
	Outcome	**Effect size [Comparison]**	**Heterogeneity**	**Indirectness,** *is my patient different from those in the study that the results cannot apply?*	**Feasibility:** *Is the treatment feasible in my setting?*	**Importance:** *Will the potential benefits outweigh the potential harms for my patient?*	
Truong et al; 2021[15]	Medication adherence	Pooled RR=2.79 (95% CI=2.26, 3.45); P<0.00001 [VDOTS vs DOTS]	I2=25% Chi2=3.98, df=3 (P=0.26)	✗	✓	✓	I
	Proportion of doses observed	Pooled MD=0.22 (95% CI=0.06, 0.39) [VDOTS vs DOTS]	I2=96% Chi2=45.25, df =2 (P<0.00001)	✗	✓	✓	II
	Treatment completion	Pooled RR=1.33 (95% CI=0.73, 2.43) [VDOTS vs DOTS]	I2=98% Chi2=90.45, df=2 (P<0.00001)	✗	✓	✓	II
	Bacteriological resolution	Pooled RR=1.06 (95% CI=1.01, 1.11) [VDOTS vs DOTS]	I2=0% Chi2=0.62, df=2 (P=0.74)	✗	✓	✓	II
Wong et al, 2022[16]	Treatment completion	Similar, ranging from RR=0.97 (95%CI=0.88–1.07) to 1.01 (95%CI=0.93–1.11) [SMS reminders vs DOTS/Self-Administered Treatment]	NR	✗	✓	✓	III
		Better, ranging from RR=1.17 (95%CI=1.06 – 1.30) to 1.72 (95%CI=1.31–2.25) [Phone reminders vs Self-Administered Treatment]	NR	✗	✓	✓	III
		Similar, from one study RR=0.91 (95%CI=0.76–1.11) [Phone reminders vs DOTS]	NR	✗	✓	✓	III
		Better, ranging from RR=0.94 (95%CI=0.78–1.14) to 1.36 (95%CI:1.19–1.55) [VDOTS vs DOTS]	NR	✗	✓	✓	III

Alipanah et al; 2018[17]	Treatment Completion	2CS of [VDOTS vs DOTS] RR= 1.17 (95%CI= 0.79-1.72)	NR	✗	✓	✓	II
		2 RCTs of Phone Reminders RR= 0.24 (95%CI= 0.01 - 7.29)	Significant heterogeneity	✗	✓	✓	I
		1 CS of Phone Reminders RR= 0.94 (95%, CI 0.84 - 1.06)	NR	✗	✓	✓	II
		1 RCT of [SMS Reminder vs DOTS] RR= 1.11 (95%, CI 1.04 - 1.18)	NR	✗	✓	✓	II
	Cure	2 RCTs of Phone reminders RR= 1.22 (95%, CI 0.78 - 1.90)	NR	✗	✓	✓	II
		1 Cs of Phone reminders RR= 2.32 (95%, CI 1.60 - 3.36)	NR	✗	✓	✓	II
	Treatment Success (sum of treatment completion and cure)	3 RCTs of Phone Reminders RR= 1.00 (95%, CI 0.97-1.04)	I2= 0% Chi2= 0.57, df= 2 (p= 0.75)	✗	✓	✓	II
	Mortality	1CS of [VDOTS vs DOTS] RR= 1.80 (95%, CI 0.19-17)	NA	✗	✓	✓	IV
		2 RCTs of Phone Reminders RR= 1.02 (95%, Ci 0.69 - 1.76)	NA	✗	✓	✓	II
		1 CS of Phone Reminder RR= 0.95 (95%, CI 0.61 - 1.47)	NA	✗	✓	✓	II
Ngwatu; 2018[18]	Treatment completion	Similar, ranging from RR: 0.99 (95% CI 0.93 - 1.05) to RR 1.47 (95% CI 0.96 - 2.25) [VDOTS vs DOTS]	NA	✗	✓	✓	III
		No significant effect, ranging from aRR: 0.71 (95% CI 0.17 - 1.13) to RR: 1.45 (95% CI 0.81 - 2.56) [SMS vs DOTS]	NA	✗	✓	✓	III
	Cure rate	Better, RR: 2.32 (95% CI 1.60 - 3.36) [MM vs DOTS]	NA	✗	✓	✓	III

Ridho; 2022[19]	Treatment completion	**VDOTS vs DOTS:** United Kingdom OR = 2.52 (95%CI = 1.17-5.54) United States RR = 1.36 (95%CI = 1.19-1.55) RR = 0.99 (95%CI = 0.93-1.05)	NA	✗	✓	✓	III
		Ingestible sensor vs DOTS: OR = 7.69 (95%CI = 4.51-14.48)	NA	✗	✓	✓	II
		SMS vs DOTS RR ranging from 0.87 (95%CI = 0.81-0.94) to 1.10 (95%CI = 1.04-1.18) OR = 1.45 (95%CI = 0.81-2.56)	NA	✗	✓	✓	III
	Treatment adherence	**VDOTS vs DOTS** RR = 1.08 (95%CI = 0.89-1.32)	NA	✗	✓	✓	III
		SMS vs DOTS RR = 1.05 (95%CI = 1.04-1.06)	NA	✗	✓	✓	III
	Cure rate	**Phone call reminder vs DOTS** RR = 1.30 (95%CI = 1.07-1.59)	NA	✗	✓	✓	III
		SMS vs DOTS OR = 1.06 (95%CI = 0.65-1.73) OR = 2.47 (95%CI = 1.13-5.43) RR = 1.05 (95%CI = 0.62-1.76)	NA	✗	✓	✓	III
Nglazi et al; 2013[20]	Completion rate	Higher, RR=3.53 (10.59% vs. 3.00%) (CI not reported) [SMS vs DOTS]	NA	✗	✓	✓	II
	Self-reported adherence	Higher, but without statistical significance, RR=1.49 (95% CI 0.90, 2.42) [SMS vs DOTS]	NA	✗	✓	✓	III
	Cure rate	Similar, RR=0.939 (62.35% vs. 66.40%) (CI not reported) [SMS vs DOTS]	NA	✗	✓	✓	III
	Treatment success	Similar, RR=1.05 (72.94% vs. 69.4%) (CI not reported) [SMS vs DOTS]	NA	✗	✓	✓	III

✓, no serious limitation; ✗, serious limitation; ?, unclear.

ARR, absolute risk reduction; ARI, absolute risk increase; CI, confidence intervals; RR, risk ratio; LOE, level of evidence; MD, mean difference; NNT/H, number needed to treat/harm; NA, not applicable; NR, not reported; DOTS, directly observed therapy; VDOTS, video directly observed therapy.