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# eHealth in TB clinical management

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SUMMARY

**BACKGROUND**: The constant expansion of internet and mobile technologies has created new opportunities in the field of eHealth, or the digital delivery of healthcare services. This TB meta-analysis aims to examine eHealth and its impact on TB clinical management in order to formulate recommendations for further development.

**METHODS**: A systematic search was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework in PubMed and Embase of articles published up to April 2021. Screening, extraction and quality assessment were performed by two independent researchers. Studies evaluating an internet and/or mobile-based eHealth intervention with an impact on TB clinical management were included. Outcomes were organised following the five domains described in the WHO "Recommendations on Digital Interventions for Health System Strengthening" guideline.

**RESULTS**: Search strategy yielded 3,873 studies, and 89 full texts were finally included. eHealth tended to enhance screening, diagnosis and treatment indicators, while being cost-effective and acceptable to users. The main challenges concern hardware malfunction and software misuse.

**CONCLUSION**: This study offers a broad overview of the innovative field of eHealth applications in TB. Different studies implementing eHealth solutions consistently reported on benefits, but also on specific challenges. eHealth is a promising field of research and could enhance clinical management of TB.

**KEY WORDS**: tuberculosis; telemedicine; respiratory; clinical

In the past 25 years, the growing availability of internet-based technologies has alteered the global landscape.[1] In 2021, 60% of the world's population has internet access, 2 billion of whom are in low-income countries, steadily closing the gap in internet and cellular access.[2] The medical world has begun to take advantage of these technologies by employing increasingly more internet and mobile solutions which expand, assist or enhance medical activities, a field known as digital health or electronic health (eHealth).[3] The WHO has recently published the "Global Strategy on Digital Health 2020–2025" report, highlighting the requirements for successful implementation of digital health, and encouraging the development of this field in a sustainable, equitable and transparent manner.[4]

Emerging technologies are especially attractive for TB, as they could provide cost-efficient, practical, innovative solutions[5–7] for an infectious disease that primarily affects low and lower-income countries.[8] However, as with every relatively new research field, interventions have been experimental, employing different technologies, and study designs, and covering multiple aspects of TB management.

The field of eHealth in TB is gaining pace, as recognised by the End TB strategy,[9] which expressly mentions the "application of novel information and communication technologies for health", in support of future eHealth developments. Furthermore, the recent guideline "Recommendations on Digital Interventions for Health System Strengthening"[10] addresses some of these issues regarding heterogeneity by offering a framework to organise, inform and guide stakeholders and policy-makers about the role of eHealth interventions in healthcare delivery.

Efforts to organise the field of eHealth in TB and to provide recommendations for future development are under way; however, recent reviews have either been narrative,[11] or focused on certain aspects of TB care.[12] This systematic review addresses multiple calls to organise this new field, including from the

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European Commission, and especially in the present global context,[13,14] and aims to offer a "birds-eye" view on implemented eHealth interventions in TB care to understand their application, opportunities and challenges in order to provide recommendations for future development of eHealth in TB care.

## METHODS

A research protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework and registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42018115440). A systematic literature search was performed of the PubMed and EMBASE databases, with a final check in April 2021.

eHealth interventions were defined as any solution which employed internet and/or mobile devices, deployed in a clinical medical setting. Two authors (IM, CL) independently screened all papers' titles and abstracts. Unresolved conflicts were resolved by a third reviewer (JWC). Covidence software (Covidence; Melbourne VIC, Australia) was used for screening and quality evaluation, MS Excel 2013 (Microsoft, Redmond, WA, USA) for data extraction and Rev Man 5.4 (Cochrane, London, UK) for meta-analysis.

### *Search queries*

Known synonyms and word clouds for "eHealth" were used in the search query. Full search query can be found in the Supplementary Data.

### *Study selection*

Inclusion criteria were usage of internet and/or mobile technologies, implementation analysis, user base with at least one of TB current or former patients, TB contacts, medical staff involved in TB clinical care (nurses, physicians, para-medical staff), with comparisons. Studies were included regardless of language used, basic demographics or type of study. Grey literature, any type of reviews, policy papers, books were excluded. For studies without full text access, the original authors were contacted.

### *Outcome measures*

Outcome measures were grouped following the WHO "Recommendations on digital interventions for health system strengthening" evidence-to-decision framework,[10] which generated the five main domains under which all outcomes were nested. Effectiveness included diagnosis and treatment indicators, such as adherence and cure rates. Acceptability referred to outcomes pertaining to user perceptions of the intervention, such as acceptability and user satisfaction with the intervention. Feasibility covered challenges and facilitators for the interventions. Resource use pertained to cost-effectiveness. Gender, rights, equality focused on privacy and patient support.

### *Data extraction and quality assessment*

Data extraction included first author, year of publication, country, type of study, type of intervention, PICO (population, intervention, comparison, outcome) criteria, and GRADE criteria for quality assessment.[15] Two authors (IM, CL) independently performed data extraction and quality assessment, where outcomes were graded by taking into consideration the overall quality of the studies included, based on the GRADE quality of evidence criteria.[16] Publication bias was analysed using funnel plots, and on an individual study basis by evaluating the publications themselves.

### *Data synthesis and analysis*

Meta-analysis was performed on studies with similar populations and outcome measures, and different analyses were performed depending on outcome: studies reporting dichotomous data were analysed using the random-effects odds ratio (OR) Mantel-Haenzel method, with their 95% confidence intervals (CIs); this model was chosen based on the assumption that there might be other factors influencing the outcome beyond the intervention itself. Studies reporting continuous data were analysed using inverse-variance random effects, and expressed in mean difference, 95% CIs. Studies reporting diagnosis accuracy were included in a diagnosis accuracy review and described as a forest plot (including specificity and sensitivity of each diagnosis method included) and a summary receiver operating characteristics (SROC) plot. All outcomes not in meta-analysis were reported as a narrative synthesis. An Excel file was compiled using all study data based on outcomes. All costs were harmonised in 2021 euros using an inflation calculator[17] and the current exchange rate.

## RESULTS

### *General results*

Search queries resulted in 3,873 studies eligible for screening, of which 89 were included in our review (Figure 1). Only six full texts (1.5%) warranted the additional opinion of a third reviewer. One study was not written in English,[18] and was translated using the authors' research network. Of the 89 studies, 17 were randomised controlled trials (RCTs), 7 cluster RCTs, 21 non-RCTs, and 44 used a "before and after" design. By country of implementation, the largest proportion of studies were from the United States ($n=12$), followed by South Africa ($n=11$).

There has been an increase in the number of studies performed as the years progressed, with a maximum of four studies published per year before 2015 to 18

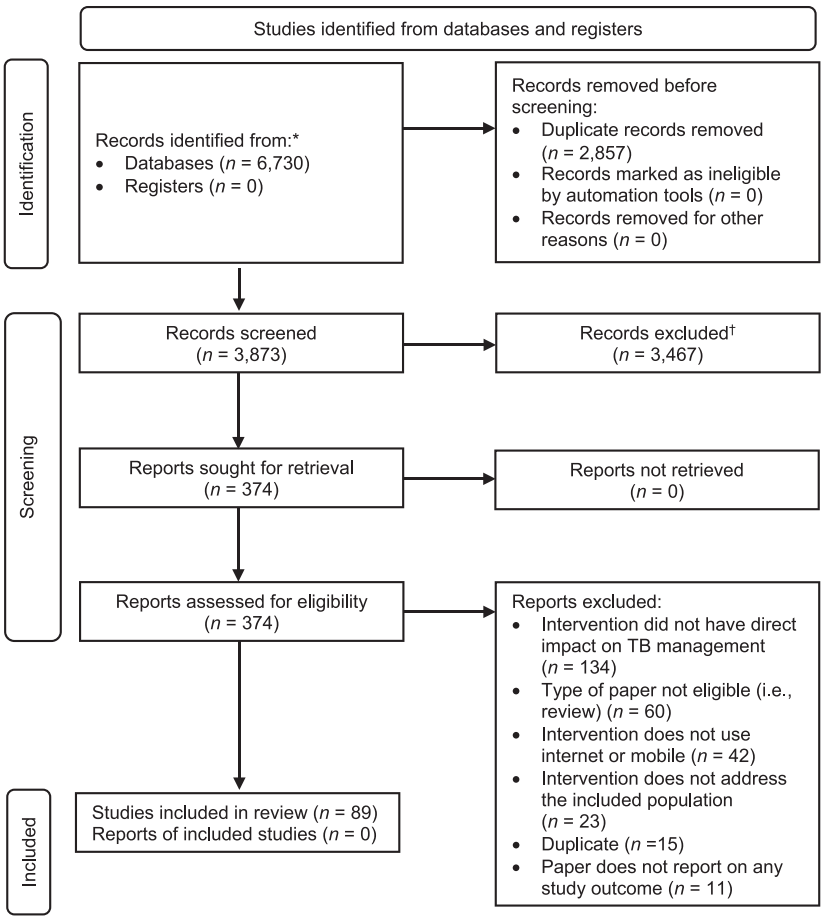


**Figure 1** PRISMA 2020 flow diagram for new systematic reviews (included searches of databases and registers only). *Consider reporting the number of records identified from each database or register searched if possible (rather than the total number across all databases/registers). †If automation tools were used, indicate how many records were excluded by a human and how many were excluded using automation tools. Source: Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

studies in 2020; the quality of the studies improved at the same time: before 2015, there were 7 (22%) cluster RCTs, but 17/57 (30%) after 2015. Using the GRADE criteria for quality of evidence, 35 (39%) had very low, 32 (36%) low, 7 (8%) moderate and 15 (17%) high. There was no clear publication bias identified as funnel plots indicate differences in results and there were negative results across studies. Of the 89 studies, 86 (93.3%) reported no conflict of interest and 3 studies reported authors setting up small academic companies to collect royalties from their proposed interventions.[19–21] The majority of studies analysed a maximum of three WHO domains, with only five reporting outcomes on all five domains (Figure 2).

### *Effectiveness domain*

eHealth tended to enhance diagnosis procedures at each step of the diagnosis cascade. Through eHealth, TB diagnoses could be made where there was a lack of expertise, with one study reporting that a remote panel of experts had helped avoid "22 wrong treatment schemes".[22] Second, our meta-analysis indicated that eHealth increased the likelihood of a person to be correctly referred, resulting in a higher chance of initiating treatment in a timely manner (Table), with one study observing that the intervention increased the number of microbiological samples correctly referred 275-fold (from 9 to 2,479).[23]

In recent years, the most robust analyses concerning diagnosis have focused on artificial intelligence/machine learning programmes dedicated to radiology, and meta-analysis suggests that these supersede standard of care (Figure 3, Supplementary Figure S1). Two studies not only compared automated diagnosis aids to genomic tests, but also to physicians, and concluded that the interventions superseded standard of care. However, studies mention several caveats, such as the fact that automated TB scoring would depend on cut-off points, and that diagnosis accuracy might be lower for certain diagnoses such as "hilar adenopathy" and "consolidation".[24]

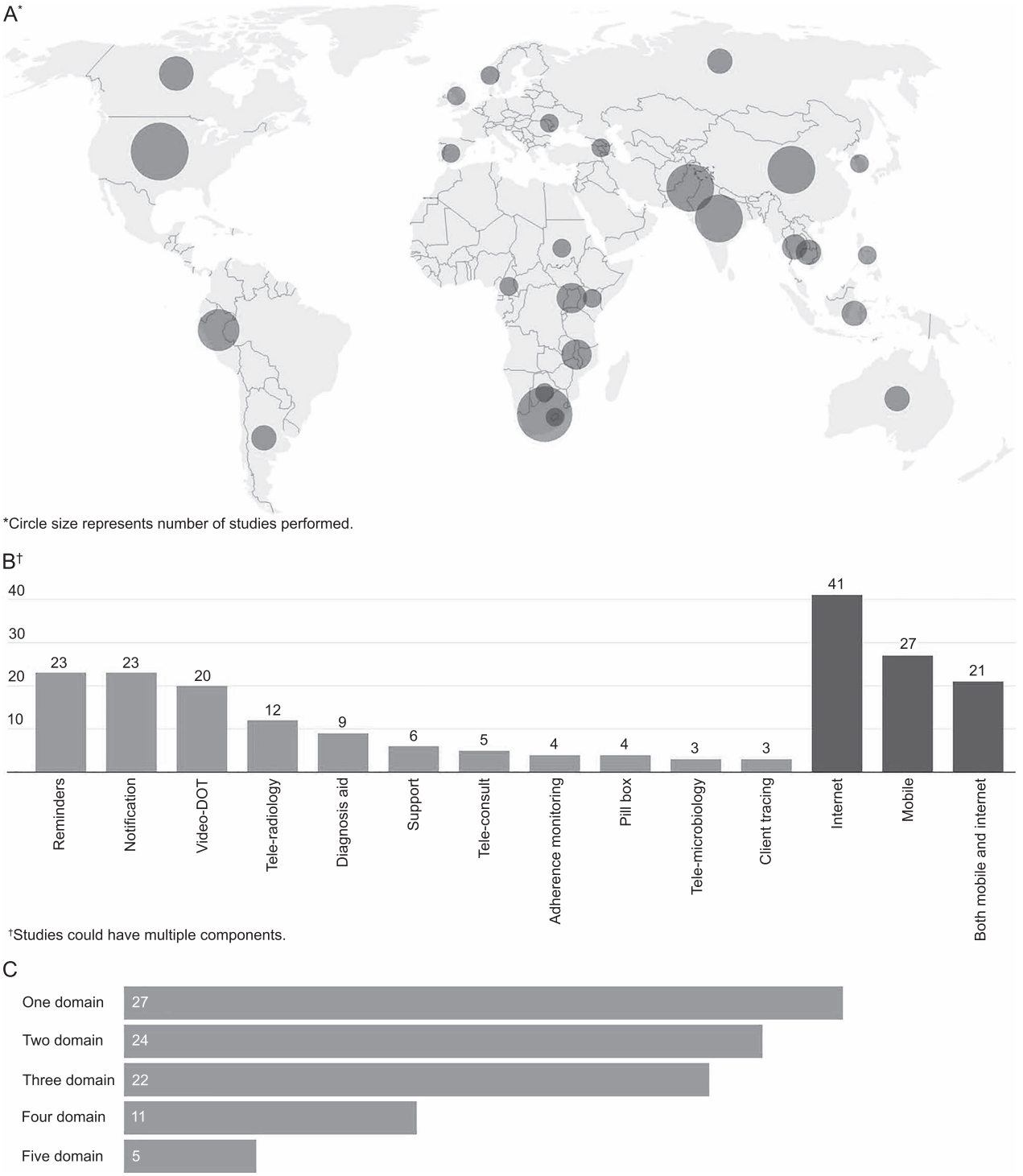


**Figure 2** Study characteristics: **A)** countries where eHealth studies were performed;* **B)** studies by intervention components;† **C)** studies analysed by WHO domain.

With regard to treatment indicators (Table, Supplementary Figures S2 and S3), digital health tended to perform better—meta-analysis results indicated that the OR of a patient completing treatment within the eHealth group was higher than standard of care and that patients in the eHealth group had a higher observable fraction overall. Furthermore, meta-analysis reports on a higher cure rate for the eHealth group. Two studies analysing the same app, 99DOTS, reported generally worse outcomes, explained by the misuse of the app by both patients and medical providers alike, which was attributed to a lack of training and dissemination.

eHealth introduction reduced error rates in medical charts and in laboratory results compared to standard of care, such as incorrect bacteriological results or

**Table** Summary of outcomes

| Quality of evidence | Outcome summary |
|---|---|
| Domain: effectiveness | |
| Referrals: moderate | 8 studies;[43–50] total events in intervention: 5,405/919,090; total events in control: 2,517/1,217,270. meta-analysis, random effects, favours intervention: OR for a person to be correctly referred in intervention vs. standard of care: 4.38 (95% CI 2.35–8.19), $\tau^2$ 0.79, $I^2 = 97\%$ |
| Diagnosis performance: moderate | 5 studies;[19,51–54] total number of patients: 17,925; meta-analysis, diagnosis accuracy, sROC analysis, radiology automated diagnosis tools tend to outperform standard of care (physician) (Figure 3). Diagnosis of TB established through sputum culture or GeneXpert (Cepheid, Sunnyvale, CA, USA) |
| Diagnosis narrative: outcomes | Tele-radiology,[55–59] tele-microscopy[60,61] with human experts aiding the diagnosis: concordance of 74.7–100% with standard of care. Automated radiology[24,62] and TST readers[29] accuracy depend on cut-off points, ranging from 20% to 95%. Automated TB diagnosis aids have sensitivity of 66.7% and 89%[30,63] |
| Patients adherence: moderate | 27 studies;[5,21,32,33,35,38,45,64–83] total events in intervention: 3,400/5,414; total events in control: 4,177/6,824; meta-analysis, OR, random effects, favours intervention: OR for a person to complete TB treatment in intervention vs. standard of care: 1.79 (95% CI 1.33–2.40), $\tau^2$ 0.35, $I^2 = 85\%$, $Z = 3.89$ |
| Adherence: FEDO: moderate | 8 studies;[5,18,21,37,67,83–85] total patients in intervention: 681; total patients in control: 704; meta-analysis, mean difference, favours intervention: patients in intervention groups had a higher observable fraction with 10.9% than standard of care (95% CI 0.75–20.97), $\tau^2$ 200, $I^2 = 99\%$, $Z = 2.11$ |
| Adherence: FEDO: narrative outcomes | FEDO reported as the same between groups by one study,[86] better in intervention groups in 7 studies,[5,37,76,87,88] and worse in intervention by one study (underutilised app because of the reported errors)[34] |
| Cure rate: moderate | 8 studies;[33,34,38,73,74,79,81,89] total events in intervention: 1,249/2,259; total events in control: 1,248/2,633; meta-analysis, OR, random effects, favours intervention: OR for patients in intervention groups to be cured 1.45 (95% CI 1.08–1.94) vs. standard of care $\tau^2$ 0.09, $I^2 = 68\%$, $Z = 2.49$ |
| Cure rate narrative | Cure rate was lower in intervention (11% vs. 30%, the app was misused by patients and health providers alike)[35] |
| Sputum conversion narrative | Patients in intervention groups had faster sputum conversion by 16 days in one study,[25] more patients had sputum conversion at 2 months in three studies.[45,78,90] One study reported that less non-MDR patients in intervention sputum converted at 2 months[90] |
| Error rate: low | There were between 10% and 97% less errors in intervention vs. standard of care (paper forms)[22,38,91,92] |
| Intervention additional benefits narrative | 13 studies;[22,30,37,66,67,70,76,85–87,93–95] in order of frequency: flexibility (4), improved communication (4), convenience (3), the possibility of individualising the intervention (2), less medical staff exposed to active cases (1), improvement of the knowledge base (1) |
| Domain: acceptability | |
| User satisfaction: low | 15 studies;[7,18,21,26,37,49,57,71,81,83,84,94,96–98] between 61% and 100% of the participants would recommend the intervention<br>90.3%;[25,85,89] users in intervention groups scored higher on satisfaction scores, 3 studies: 99.5% vs. 99.2%, 100% vs. 70%; 92% vs. 88%<br>3 studies;[70,86,87] narrative: "Satisfaction in intervention groups 3.29 higher than control",[87] "high satisfaction in intervention group",[57,72,86] "overall, satisfaction was higher in intervention than in control"[70] |
| Intervention perceived usefulness: low | 10 studies;[20,21,32,71,73,75,81,82,95–97] between 79% and 100% found intervention useful<br>Medical staff agreed intervention was useful, 1 study;[99] more users in intervention groups found the intervention useful, 2 studies: 96% vs. 56.6%, 80% vs 32%[71,81]<br>2 studies;[32,92] usefulness scores: 7.5/10 and 7.7/10 |
| Domain: feasibility | |
| Hardware challenges narrative | Most frequent hardware challenges: broken equipment or dead batteries, 7 studies:[68,72,75,76,88,94,97] shared phones, 4 studies: stolen phone, 2 studies: [75,100] |
| Software challenges: low | Software-related incidents, 9 studies: up to 10% (0.7–8%) of missed videos or messages;[18,20,26,33,59,68,76,97,101,102] software challenges: messages not sent, 2 studies[46,103] consults not being performed, 1 study (initially 25%, dropped to 8% after learning curve[47] "system freeze", "software quirks", "server down"[18,20,26,33,59,68,76,97,101,102] |
| Network/electricity challenges: very low | Network-related issues, 17 studies: interruptions between 2 days and 8 weeks, "lower adherence correlated with poor network coverage", "slow internet"[20,30,32,37,50,59,72,75,76,85,86,88,92,94,97,103,104]<br>4 studies;[66,75,88,97] reports on electricity outages causing issues "for several participants" |
| User base-specific challenges narrative: very low | Lack of comprehension/training about the intervention, 10 studies[20,34,66,68,75,76,88,93,97] not knowing phone number, 4 studies[47,50,75,100] preference for face-to-face contact, 5 studies[33,35,46,60,80,86] scheduling conflicts and forgetfulness, 4 studies,[18,76,85,94] other user challenges, 3 studies: "more interest in computers than in the intervention", "no trickle-down effect"[21,22,91] |
| Domain: resource use | |
| Cost-saving: low | Medical facilities saved costs, 3 studies: between €13.5 and €13,495.7 per patient in travel and personnel costs;[5,7,20,62,65,84,85,102,105,106] patients saved costs, 4 studies: between €1.5 and €75 in travel costs;[71,81,87,106] costs saving, other: the break-even point would be 2.9–5.5 years,[101] "if one is willing to pay $2, the probability of cost-effectiveness rises to almost 90%",[37] costs per session associated with live vDOT (€6.54), recorded-vDOT (€5.35), clinic DOT (€8.46) and field-DOT (€19.83)[106] |

**Table** (*continued*)

| Quality of evidence | Outcome summary |
|---|---|
| Mileage-saving: low | Saved 2,368 km and 454.93 km per patient. 2 studies,[85,103] interventions are especially useful where travel would be a necessity; 7 studies[7,21,22,32,39,76,94] |
| Capacity-saving: low | 6 studies;[39,43,44,50,76,102] interventions allowed medical facilities to increase their capacity ("see more patients"): between 100% and 208% |
| Time-saving: moderate | 5 studies;[5,18,81,92,106] total patients in intervention: 2,042; total patients in control: 3,139; meta-analysis, mean difference, favours intervention: intervention consults and observed doses were faster with a mean difference of 11.25 min (95% CI 8.57–13.92) than standard of care, $\tau^2$ 14.28, $I^2 = 99\%$, $Z = 8.24$ |
| Time-saving narrative | Saved time, 4 studies, 2.93–3.1 min saved per sample,[101] between 19.7 min and 3.24 h saved per consult[22,23,25,26,38,39,44,57,59,70,71,86,87,102,107,108] less visits per patient were required in intervention: from 38,160 to 4,604 (decrease of 87.9%).[99]1 study: intervention was 7x slower (small field of view in tele-microscopy)[60] |
| Domain: gender, equality, rights | |
| Education: very low | Increase knowledge scores, 2 studies: of 12%, 21%;[75,96] No difference in knowledge scores: 3 studies[30,64,73] |
| Patient support narrative | Patients felt "cared for by staff",[32,80] "80.9% family supporters reported that phone calls helped them feel confident that the disease was under control"[89], 1 study mentions no difference in support levels between intervention and control[82] |
| Privacy: low | 3 studies;[26,37,71] 2–27% of users worried about privacy breaches<br>56.6–100% users felt the intervention was better at protecting their privacy than control[7,18,20,21,30,49,70,71,84–86,101]<br>8 studies;[21,26,32,49,66,75,90,95] there were zero privacy breaches for 819 participants (vs. one privacy breach in one study in the control group) |

OR = odds ratio; CI = confidence interval; sROC = summary receiver operating characteristic; TST = tuberculin skin test; FEDO = fraction of observed dose; vDOT = video directly observed therapy.

medication doses. Various studies also noted additional benefits of eHealth interventions such as "less paperwork", "automatic response to frequent questions", "viewing all patient information on one page", "fewer nurses exposed to TB" and "increased reporting of side effects".

### *Acceptability domain*

Overall, users were satisfied with the interventions, measured either qualitatively or quantitatively. Satisfaction scores were higher in intervention groups and most participants would prefer or would recommend the interventions (Figure 4). Most users perceived the interventions as useful.

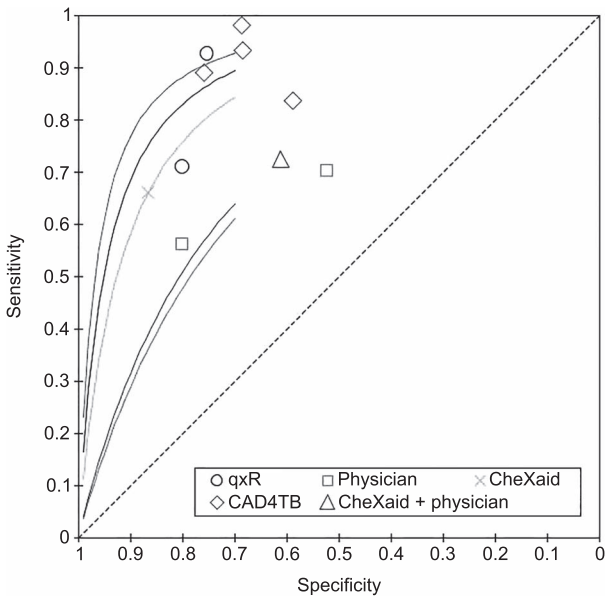


**Figure 3** sROC plot of automated X-ray diagnosis aids. sROC = summary receiver operating characteristic.

### *Feasibility domain*

Four main types of challenges were reported by studies: hardware, software, network/electricity and user base. Hardware availability was reported as an issue in a minority of cases, with most users experiencing malfunction or battery drain. Software issues were easier to resolve, with one study mentioning that there were "1.13 technical issues a month, which the medical staff could fix themselves",[25] and another that "use improved with experience".[26] Network interruptions and limited internet bandwidth caused several studies to report issues with data transmission; however, out of 17 studies reporting on these issues, 15 were before 2020. The most important user-related challenge is not understanding how the intervention works, with one study mentioning that "problems were resolved in 77.6–91.8% of cases" through training. In one study with automated SMS reminders, 28% of users did not always understand the message due to technical language.

### *Resource use domain*

None of the included studies concluded that eHealth interventions are more costly than standard of care, with all reporting various degrees of savings, depending on the local economy and travel time, translated in work hours saved, and resources it would take to reach the patients (Figure 5).

Interventions also saved time, the most notable differences being in communicating between different

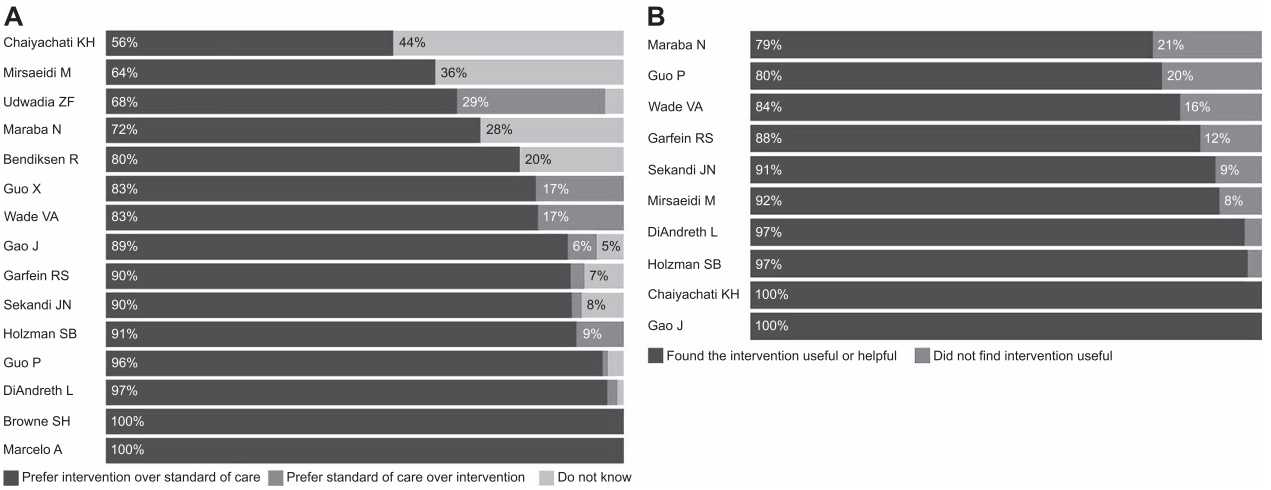


**Figure 4** Users who prefer interventions and who find interventions useful: **A)** percentage of participants who prefer interventions over standard of care; **B)** percentage of participants who found interventions useful.

medical specialties, particularly when results were sent and consultations performed via postal services. Furthermore, as indicated also by our results, interventions reduced travel and consultation time in case of directly observed therapy, which, in turn, led some facilities to attend to more patients per unit of time.

Studies mentioned that patients felt "cared for by staff": "80.9% family supporters reported that phone calls helped them feel confident that the disease was under control". Intervention users generally believed that the intervention offered greater privacy than standard of care; there were no reports of breaches of confidentiality in the studies.

## DISCUSSION

This systematic review evaluated eHealth applicability for TB prevention and treatment using the framework of the "Recommendations on digital interventions for health system strengthening" and aggregated data from 89 clinical trials. With the passage of time, research in the subject expanded, the field got more established, and studies became more rigorous. This phenomenon was observed by another systematic review.[12]

Overall, interventions tended to be non-inferior or perform slightly better regarding diagnosis and

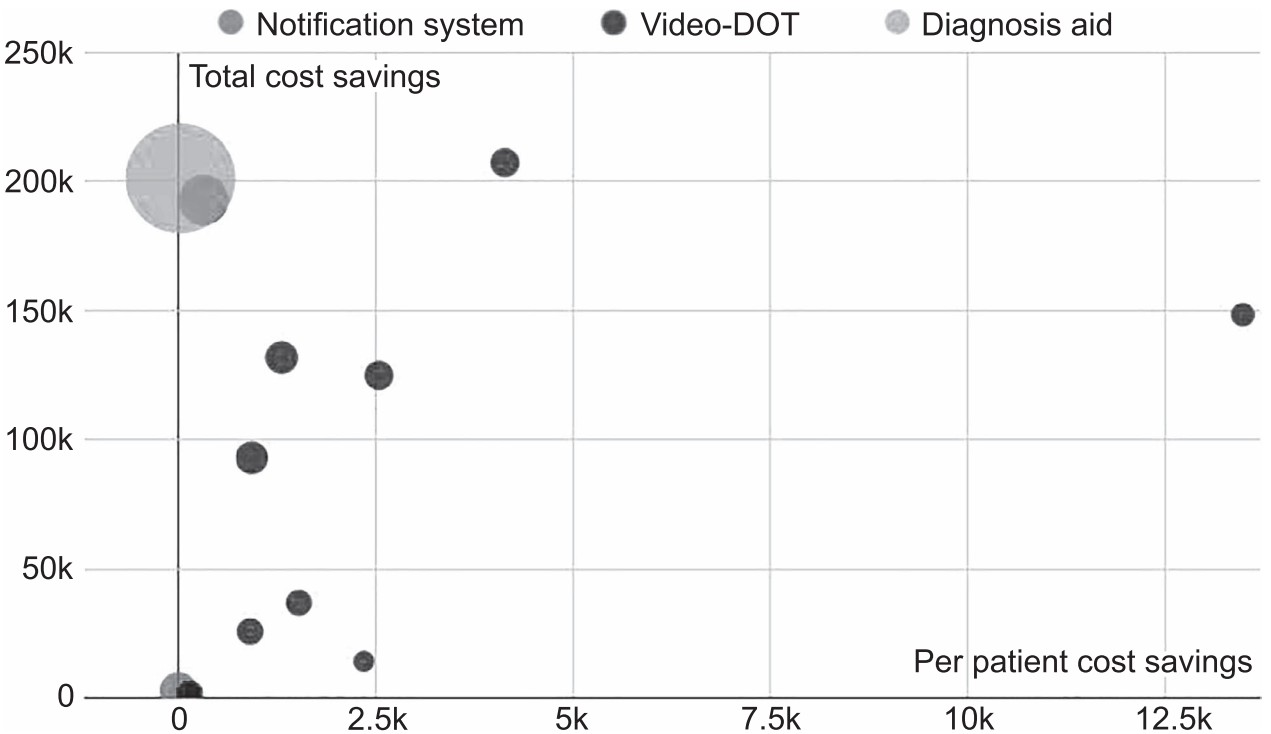


**Figure 5** Cost-savings of medical facilities. vDOT = video directly observed therapy.

treatment indicators. An earlier systematic review investigated the role of mobile phones in HIV-TB management, which demonstrated a positive effect on medication adherence,[27] while another systematic review found no difference in adherence.[28] Unsurprisingly, effectiveness of interventions depends on the setting and level of care in which they are tested.

Results suggest that diagnosis using tele-medicine are feasible to implement in current practice, especially in locations lacking TB expertise. Other diagnosis apps, such as the automated tuberculin skin test reader, can be used only with the aid of skilled medical personnel.[29] To note, medical chart error rate dropped in all studies which quantified it, and additional benefits, such as reduced workloads, were mentioned as early as 1999: "electronic information resources eliminated bulky manuals and charts. Nurses also reported greater empowerment".[30]

Benefits felt by users were reflected in the acceptability domain, where the majority of users found interventions useful and more satisfactory than standard of care. This could be especially relevant in the current context of the COVID-19 pandemic, which has reduced potential and current patient's healthcare access, leading to a decrease in TB detection and a loss of adherence.[31] One study specifically included extensively drug-resistant patients in danger of losing medication and consultations during the COVID-19 crisis in India and concluded that "while inexpensive and expedient, telemedicine may risk compromising the quality of care associated with a physical examination; however, in times of COVID-19, this is a trade-off we may have to accept." However, if we analyse healthcare worker and patient user preference for face-to-face contact under the "acceptability" domain, we note that there is a minority of studies with users citing this preference.

Implementing eHealth is not without its challenges; this has also been mentioned by an analysis of the landscape and research priorities in eHealth.[11] Overall, impactful hardware issues happened primarily in low and middle-income countries, besides dead phone batteries which happened everywhere. Stolen, broken, shared, or not having a phone were noted in six low-income countries (LICs) and 11 middle-income countries (MICs). The same distribution was observed for network failures, with only 6/17 studies being conducted in high-income countries. Electricity outages all happened in LICs or MICs.

User-related challenges were reported by most studies and were the most diverse, ranging from users not knowing their own phone number[32,33] to "the requesting physician appeared to take more interest in computers than in the medical diagnosis".[22] Regarding the user base, multiple studies noted that successful implementation was dependent on the user's tech savviness and, barring that, their education. The best example of this cautionary tale is the 99DOTS app, with multiple studies reporting that its misuse and underuse because of a lack of training led to inefficiencies in its implementation.[34,35]

The domain where eHealth shined was cost-effectiveness. Introduction of medication monitors and video-observed therapy were expected to lead to substantial cost savings.[36] This forecast was supported by the results presented in the resource use domain, with considerable savings per patient, especially in travel time and costs for either the patient or medical staff, but also because internet consultations tended to be more efficient, with one nurse noting "it was easier to finish videophone visits, as the patients did not try to prolong calls by offering a cup of tea or social interaction".[37] Furthermore, interventions also led to streamlined sample transportation and result communication so much so that one study reported that "because of the delay, patients as well as his or her physicians often forgot that they had ever performed a culture" before eHealth implementation.[38] Finally, eHealth tended to make better use of human resources, with one study specifically mentioning that the capacity of medical facilities increased, "without a reduction in the volume of [control] encounters".[39]

A minority of patients mentioned being worried about privacy breaches, but the majority consider digital health to be safer than controls. One study noted that while 58% of medical staff worried about unintentional disclosure of private files, 87% of patients were not worried at all about confidentiality breaches. There were no reported breaches of privacy in the studies included (vs. one in a control group). It appears that if professionals approach eHealth in TB care with the same rigour they approach any other professional medical data, users can trust them to keep their data confidential.

Last but not least, as TB is a stigmatising, lonely disease,[40] it is important to highlight the studies which reported that patients "no longer felt isolated",[41] "were happy when receiving motivational texts",[42] and felt "cared for by staff".[32] However, no studies reported on gender, sexual or race inequalities.

Overall, it is important to note that while eHealth was at least non-inferior concerning effectiveness, users trusted and were satisfied with the interventions; eHealth implementation was also cost-effective if potential challenges are taken into account. eHealth interventions could be especially relevant in the current context.

### *Strengths*

This systematic review organises a broad body of evidence and offers an overview of the five WHO domains for analysing eHealth. The focus of this review was clinical care, and by analysing the interplay between the five domains, it can offer guidance on the challenges to be resolved before

implementing eHealth and provide information on potential benefits, especially those pertaining to user perception, patient data safety and cost-effectiveness.

### *Limitations*

As eHealth is a relatively new field, earlier studies tended to have a historical cohort or the same cohort as a comparison group. Also, methods to analyse eHealth impact have evolved, from simple interviews to standardised questionnaires and economic analysis. However, only five studies analysed all WHO domains. Grey literature was not accessed, as a cursory search revealed that it tended to skim on outcome reporting. Quality of evidence varied, with the best evidence in the effectiveness domain, and the least in the gender, equality and rights domain.

## CONCLUSION

eHealth adoption in TB is growing and most eHealth interventions fulfil the five WHO domains goals. Interventions tended to add value to standard of care, measured by "hard" indicators of effectiveness and resource use, but also by "soft" indicators of acceptability. eHealth interventions are especially useful where travel is required and in settings with a lack of resources and expertise. However, infrastructure, experience and training are needed to ensure that eHealth is effective. Nevertheless, as the global trend is towards the increasing use of technology in everyday life, users will become savvier, health interventions will become more readily available, and evidence more robust and reliable.

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### *References*

1 PC Plus. Looking back at more than 25 years of the World Wide Web, August 06, 2016. https://www.techradar.com/news/internet/web/celebrating-20-years-of-the-world-wide-web-615150
2 International Telecommunication Union. Measuring the information society: report. Vol 1. Geneva, Switzerland: ITU, 2018.
3 Oh H, et al. What is eHealth (3): a systematic review of published definitions. J Med Internet Res 2005;7(1):e1.
4 World Health Organization. Draft global strategy on digital health 2020–2025. Geneva, Switzerland:WHO, 2020.
5 Story A, et al. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial. Lancet 2019;393(10177):1216–1224.
6 Angel DI, et al. Cutaneous tuberculosis diagnosis in an inhospitable Amazonian region by means of telemedicine and molecular biology. J Am Acad Dermatol 2005;52(5Suppl 1):S65–68.
7 Mirsaeidi M, et al. Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective. Eur Respir J 2015;46(3):871–874.
8 World Health Organization. Tuberculosis (TB). Geneva, Switzerland: WHO, 2021.
9 World Health Organisation. The End TB Strategy. Geneva, Switzerland: WHO, 2021.
10 World Health Organisation. Guideline: recommendations on digital interventions for health system strengthening. Geneva, Switzerland: WHO, 2019.
11 Subbaraman R, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ Glob Health 2018;3(5):e001018.
12 Lee S, et al. Toward developing a standardized core set of outcome measures in mobile health interventions for tuberculosis management: systematic review. JMIR Mhealth Uhealth 2019;7(2):e12385.
13 Ricciardi W. Assessing the impact of digital transformation of health services: opinion by the Expert Panel on Effective Ways of Investing in Health (EXPH). Eur J Public Health;29(Supplement_4):279.
14 Budd J, et al. Digital technologies in the public-health response to COVID-19. Nat Med 2020;26(8):1183–1192.
15 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. London, UK: John Wiley & Sons, 2019: p 672.
16 BMJ Best Practice. What is GRADE? London, UK: BMJ, 2017. https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/
17 Inflation Calculator. http://officialdata.org Accessed August 2021.
18 Bendiksen R, et al. Use of video directly observed treatment for tuberculosis in Northern Norway. Tidsskr Nor Laegeforen 2020;140(1). [Article in English, Norwegian]
19 Khan FA, et al. Chest x-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: a prospective study of diagnostic accuracy for culture-confirmed disease. Lancet Digital Health 2020;2(11):e573–e581.
20 Holzman SB, et al. Use of smartphone-based video directly observed therapy (vDOT) in tuberculosis care: single-arm, prospective feasibility study. JMIR Form Res 2019;3(3):e13411.
21 Holzman SB, Zenilman A, Shah M. Advancing patient-centered care in tuberculosis management: a mixed-methods appraisal of video directly observed therapy. Open Forum Infect Dis 2018;5(4):ofy046.
22 Uldal SB, et al. Using e-mail in the management of tuberculosis patients, north-west Russia. Int J Tuberc Lung Dis 2005;9(12):1367–1372.
23 Palupi S, et al. SITRUST app: detecting TB cases and increasing RMT utilization in the healthcare facilities in East Java. Indian J Public Health Res Dev 2019;10(3):453–458.
24 Madhani F, et al. Automated chest radiography and mass systematic screening for tuberculosis. Int J Tuberc Lung Dis 2020;24(7):665–673.
25 Blaya JA, et al. Reducing communication delays and improving quality of care with a tuberculosis laboratory information system in resource poor environments: a cluster randomized controlled trial. PLoS ONE 2014;9(4):e90110.
26 Maraba N, et al. Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: results from a pilot study. PLoS One 2018;13(7):e0199687.

27 Devi BR, et al. mHealth: an updated systematic review with a focus on HIV/AIDS and tuberculosis long term management using mobile phones. Comput Methods Programs Biomed 2015;122(2):257–265.
28 Ngwatu BK, et al. The impact of digital health technologies on tuberculosis treatment: a systematic review. Eur Respir J 218;51(1):1701596.
29 Moayedi-Nia S, et al. The mTST - an mHealth approach for training and quality assurance of tuberculin skin test administration and reading. PLoS One 2019;14(4):e0215240.
30 Hripcsak G, et al. A health information network for managing innercity tuberculosis:bridging clinical care, public health, and home care. Comput Biomed Res 1999;32(1):67–76.
31 McQuaid CF, et al. The impact of COVID-19 on TB: a review of the data. Int J Tuberc Lung Dis 2021;25(6):436–446.
32 Iribarren S, et al. TextTB: a mixed method pilot study evaluating acceptance, feasibility, and exploring initial efficacy of a text messaging intervention to support TB treatment adherence. Tuberc Res Treat 2013;2013:349394.
33 Mohammed S, Glennerster R, Khan AJ. Impact of a daily SMS medication reminder system on tuberculosis treatment outcomes: a randomized controlled trial. PLoS One 2016;11(11):e0162944.
34 Prabhu A, et al. "99DOTS"techno-supervision for tuberculosis treatment – a boon or a bane? Exploring challenges in its implementation at a tertiary centre in Delhi, India. Indian J Tuberc 2020;67(1):46–53.
35 Thekkur P, et al. 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. Glob Health Action 2019;12(1):1568826.
36 Nsengiyumva NP, et al. Evaluating the potential costs and impact of digital health technologies for tuberculosis treatment support. Eur Respir J 2018;52(5):1801363.
37 Wade VA, et al. Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. PLoS One 2012;7(11):e50155.
38 Lee JE, et al. What strategy can be applied to the patients with culture positive tuberculosis to reduce treatment delay in a private tertiary healthcare center? Infect Chemother 2011;43(1):42–47.
39 Strymish J, et al. Electronic consultations (E-consults): Advancing infectious disease care in a large veterans affairs healthcare system. Clin Infect Dis 2017;64(8):1123–1125.
40 Cremers AL, et al. Assessing the consequences of stigma for tuberculosis patients in urban Zambia. PLoS One 2015;10(3):e0119861.
41 Hoffman JA, et al. Mobile direct observation treatment for tuberculosis patients: a technical feasibility pilot using mobile phones in Nairobi, Kenya. Am J Prev Med 2010;39(1):78–80.
42 Nhavoto JA, Grönlund Å, Klein GO. Mobile health treatment support intervention for HIV and tuberculosis in Mozambique: perspectives of patients and healthcare workers. PLoS One 2017;12(4):e0176051.
43 Wang L, et al. Model collaboration between hospitals and public health system to improve tuberculosis control in China. Int J Tuberc Lung Dis 2009;13(12):1486–1492.
44 Chadha S, et al. Using mhealth to enhance TB referrals in a tribal district of India. Public Health Action 2017;7(2):123–126.
45 Long R, et al. Do "virtual" and "outpatient" public health tuberculosis clinics perform equally well? A program-wide evaluation in Alberta, Canada. PLoS One 2015;10(12):e0144784.
46 Davis JL, et al. Home-based tuberculosis contact investigation in Uganda: a household randomised trial. ERJ Open Res 2019;5(3):00112-2019.
47 Wagstaff A, van Doorslaer E, Burger R. SMS nudges as a tool to reduce tuberculosis treatment delay and pre-treatment loss to follow-up. A randomized controlled trial. PLoS One 2019;14(6):e0218527.
48 Choun K, et al. Using mobile phones to ensure that referred tuberculosis patients reach their treatment facilities: a call that makes a difference. BMC Health Serv Res 2017;17(1):575.
49 DiAndreth L, et al. Secure delivery of HIV-related and tuberculosis laboratory results to patient cell phones: a pilot comparative study. AIDS Behav 2020;24(12):3511–3521.
50 Khan AJ, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis 2012;12(8):608–616.
51 Philipsen RHHM, et al. Automated chest X-ray reading for tuberculosis in the Philippines to improve case detection: a cohort study. Int J Tuberc Lung Dis 2019;23(7):805–810.
52 Nash M, et al. Deep learning, computer-aided radiography reading for tuberculosis: a diagnostic accuracy study from a tertiary hospital in India. Sci Rep 2020;10(1):210.
53 Rajpurkar P, et al. CheXaid: deep learning assistance for physician diagnosis of tuberculosis using chest x-rays in patients with HIV. NPJ Digit Med 2020;3:115.
54 Habib SS, et al. Evaluation of computer aided detection of tuberculosis on chest radiography among people with diabetes in Karachi Pakistan. Sci Rep 2020;10(1):6276.
55 Schwab K, et al. Remote training and oversight of sonography for human immunodeficiency virus-associated tuberculosis in Malawi. J Am Coll Radiol 2019;16(2):228–232.
56 Corr P, et al. A simple telemedicine system using a digital camera. J Telemed Telecare 2000;6(4):233–236.
57 Marcelo A, et al. An online method for diagnosis of difficult TB cases for developing countries. Stud Health Technol Inform 2011;164:168–173.
58 Coulborn RM, et al. Feasibility of using teleradiology to improve tuberculosis screening and case management in a district hospital in Malawi. Bull World Health Organ 2012;90(9):705–711.
59 Corr P. Teleradiology in KwaZulu-Natal. A pilot project. S Afr Med J 1998;88(1):48–49.
60 Prieto-Egido I, et al. Design of new procedures for diagnosing prevalent diseases using a low-cost telemicroscopy system. Telemed J E Health 2016;22(11):952–959.
61 Zimic M, et al. Can the power of mobile phones be used to improve tuberculosis diagnosis in developing countries? Trans R Soc Trop Med Hyg 2009;103(6):638–640.
62 Murphy K, et al. Computer aided detection of tuberculosis on chest radiographs: an evaluation of the CAD4TB v6 system. Sci Rep 2020;10(1):5492.
63 Bavdekar SB, Pawar M. Evaluation of an internet-delivered pediatric diagnosis support system (ISABEL®) in a tertiary care center in India. Indian Pediatr 2005;42(11):1086.
64 Kumboyono K. Short message service as an alternative in the drug consumption evaluation of persons with tuberculosis in Malang, Indonesia. Japan J Nurs Sci 2017;14(2):112–116.
65 Holzschuh EL, et al. Use of video directly observed therapy for treatment of latent tuberculosis infection - Johnson County, Kansas, 2015. MMWR Morb Mortal Wkly Rep 2017;66(14):387–389.
66 Hirsch-Moverman Y, et al. Using mhealth for HIV/TB treatment support in Lesotho: enhancing patient-provider communication in the start study. J Acquir Immune Defic Syndr 2017;74:S37–S43.
67 Johnston JC, et al. The effect of text messaging on latent tuberculosis treatment adherence: a randomised controlled trial. Eur Respir J 2018;51(2):1701488.
68 Lam CK, et al. Using video technology to increase treatment completion for patients with latent tuberculosis infection on 3-month isoniazid and rifapentine: an implementation study. J Med Internet Res 2018;20(11):e287.

69 Bassett IV, et al. Sizanani: a randomized trial of health system navigators to improve linkage to HIV and TB care in South Africa. J Acquir Immune Defic Syndr 2016;73(2):154–160.
70 Chen S-H, et al. Advantage in privacy protection by using synchronous video observed treatment enhances treatment adherence among patients with latent tuberculosis infection. J Infect Public Health 2020;13(9):1354–1359.
71 Guo X, et al. A comprehensive app that improves tuberculosis treatment management through video-observed therapy: usability study. JMIR Mhealth Uhealth 2020;8(7):e17658.
72 Ratchakit-Nedsuwan R, et al. Ensuring tuberculosis treatment adherence with a mobile-based CARE-call system in Thailand: a pilot study. Infect Dis 2020;52(2):121–129.
73 Ali AOA, Prins MH. Mobile health to improve adherence to tuberculosis treatment in Khartoum state, Sudan. J Public Health Africa 2019;10(2):1101.
74 Farooqi RJ, Ashraf S, Zaman M. The role of mobile SMS-reminders in improving drugs compliance in patients receiving anti-TB treatment from DOTS program. J Postgrad Med Inst 2017;31(2):156–162.
75 Hermans SM, et al. Text messaging to decrease tuberculosis treatment attrition in TB-HIV coinfection in Uganda. Patient Prefer Adherence 2017;11:1479–1487.
76 Chuck C, et al. Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. Int J Tuberc Lung Dis 2016;20(5):588–593.
77 Belknap R, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. Ann Intern Med 2017;167(10):689.
78 Fang X-H, et al. Effect of short message service on management of pulmonary tuberculosis patients in Anhui Province, China: a prospective, randomized, controlled study. Med Sci Monit 2017;23:2465–2469.
79 Yoeli E, et al. Digital health support in treatment for tuberculosis. N Engl J Med 2019;381(10):986–987.
80 Das Gupta D, et al. Choice-based reminder cues: findings from an mHealth study to improve tuberculosis (TB) treatment adherence among the urban poor in India. World Med Health Policy 2020;12(2):163–181.
81 Guo P, et al Telemedicine technologies and tuberculosis management: a randomized controlled trial. Telemed J E Health 2020;26(9):1150–1156.
82 Khachadourian V, et al. People-centred care versus clinic–based DOT for continuation phase TB treatment in Armenia: a cluster randomized trial. BMC Pulm Med 2020;20(1):1–10.
83 Browne SH, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: a randomized controlled trial. PLoS Med 2019;16(10):e1002891.
84 Garfein RS, et al. Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study. Int J Tuberc Lung Dis 2015;19(9):1057–1064.
85 DeMaio J, Schwartz L, Cooley P, Tice A. The application of telemedicine technology to a directly observed therapy program for tuberculosis: a pilot project. Clin Infect Dis 2001;33(12):2082–2084.
86 Gassanov MA, et al. The use of videophone for directly observed therapy for the treatment of tuberculosis. Can J Public Health 2013;104(3):e272.
87 Ravenscroft L, et al. Video-observed therapy and medication adherence for tuberculosis patients: randomised controlled trial in Moldova. Eur Respir J 2020;56(2):2000493.
88 Liu X, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: a cluster-randomised trial. PLoS Med 2015;12(9):e1001876.
89 Bediang G, et al. SMS reminders to improve adherence and cure of tuberculosis patients in Cameroon (TB-SMS Cameroon): a randomised controlled trial. BMC Public Health 2018;18(1):583.
90 Kunawararak P, et al. Tuberculosis treatment with mobile-phone medication reminders in northern Thailand. Southeast Asian J Trop Med Public Health 2011;42(6):1444–1451.
91 Blaya JA, et al. Electronic laboratory system reduces errors in National Tuberculosis Program: a cluster randomized controlled trial. Int J Tuberc Lung Dis 2010;14(8):1009–1015.
92 Ha YP, et al. Evaluation of a mobile health approach to tuberculosis contact tracing in Botswana. J Health Commun 2016;21(10):1115–1121.
93 Choi SS, et al. Implementation and initial evaluation of a Web-based nurse order entry system for multidrug-resistant tuberculosis patients in Peru. Stud Health Technol Inform 2004;107(Pt 1):202–206.
94 Chaiyachati KH, et al. 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. PLoS One 2013;8(5):e64662.
95 Hodges J, et al. Implementation of a mobile health strategy to improve linkage to and engagement with HIV care for people living with HIV, tuberculosis, and substance use in Irkutsk, Siberia. AIDS Patient Care STDS 2021;35(3):84–91.
96 Gao J, Cook VJ, Mayhew M. Preventing tuberculosis in a low incidence setting: evaluation of a multi-lingual, online, educational video on latent tuberculosis. J Immigr Minor Health 2018;20(3):687–696.
97 Sekandi JN, et al. Video directly observed therapy for supporting and monitoring adherence to tuberculosis treatment in Uganda: a pilot cohort study. ERJ Open Res 2020;6(1):00175-2019.
98 Udwadia ZF, et al. Effective use of telemedicine in Mumbai with a cohort of extensively drug-resistant "XDR" tuberculosis patients on bedaquiline during COVID-19 pandemic. Lung India 2021;38(1):98–99.
99 Wang N, et al. Using electronic medication monitoring to guide differential management of tuberculosis patients at the community level in China. BMC Infect Dis 2019;19(1):844.
100 Iribarren SJ, et al. Smartphone applications to support tuberculosis prevention and treatment: review and evaluation. JMIR Mhealth Uhealth 2016;4(2):e25.
101 Blaya JA, et al. Cost and implementation analysis of a personal digital assistant system for laboratory data collection. Int J Tuberc Lung Dis 2008;12(8):921–927.
102 Mahmud N, Rodriguez J, Nesbit J. A text message-based intervention to bridge the healthcare communication gap in the rural developing world. Technol Health Care 2010;18(2):137–144.
103 Schulz TR, et al. Telehealth: experience of the first 120 consultations delivered from a new refugee telehealth clinic. Intern Med J 2014;44(10):981–985.
104 Garfein RS, et al. Tuberculosis treatment monitoring by video directly observed therapy in 5 health districts, California, USA. Emerg Infect Dis 2018;24(10):1806–1815.
105 Buchman T, Cabello C. A new method to directly observe tuberculosis treatment: skype observed therapy, a patient-centered approach. J Public Health Manag Pract 2017;23(2):175–177.
106 Asay GRB, et al. Cost of tuberculosis therapy directly observed on video for health departments and patients in New York City; San Francisco, California; and Rhode Island (2017–2018). Am J Public Health 2020;110(11):1696–1703.
107 Lorent N, et al. Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy. PLoS One 2014;9(3):e92754.
108 Farley JE, et al. Evaluation of miLINC to shorten time to treatment for rifampicin-resistant *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis 2019;23(9):980–988.

## RÉSUMÉ

**CONTEXTE : L'expansion constante d'Internet et des technologies mobiles a créé de nouvelles opportunités en matière d'e-Santé ou de fourniture numérique de services de santé. Cette méta-analyse sur la TB s'est penchée sur les solutions d'e-Santé et leur impact sur la prise en charge clinique de la TB afin de formuler des recommandations en faveur de leur développement.**

**MÉTHODES : Une analyse systématique des articles publiés jusqu'en avril 2021 a été réalisée sur PubMed et Embase, en utilisant la liste PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*). L'examen, la sélection et l'évaluation de qualité des articles ont été réalisés par deux investigateurs indépendants. Les études ayant évalué une intervention d'e-Santé sur Internet et/ou sur mobile avec un impact sur la prise en charge clinique de la TB ont été incluses. Les résultats ont été organisés selon les cinq domaines décrits dans les recommandations de l'OMS intitulées « Recommendations on Digital Interventions for Health System Strengthening ».**

**RÉSULTATS : Nous avons identifié 3 873 études, et 89 textes entiers ont finalement été inclus. Les solutions de e-Santé avaient tendance à renforcer les indicateurs relatifs au dépistage, au diagnostic et au traitement, tout en étant rentables et acceptables pour les utilisateurs. Les problèmes principaux étaient dysfonctionnement du matériel informatique et mauvaise utilisation des logiciels.**

**CONCLUSION : Cette étude fournit un vaste aperçu du domaine innovant que représentent les applications de e-Santé pour la TB. Plusieurs études ayant mis en place des solutions de e-Santé en ont rapporté les avantages, mais aussi les problèmes spécifiques. L'e-Santé est un domaine de recherche prometteur et pourrait permettre de renforcer la prise en charge clinique de la TB.**