Evaluating the potential costs and impact of digital health technologies for tuberculosis treatment support

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ABSTRACT Ensuring adherence and support during treatment of tuberculosis (TB) is a major public health challenge. Digital health technologies could help improve treatment outcomes. We considered their potential cost and impact on treatment for active or latent TB in Brazil.

Decision analysis models simulated two adult cohorts with 1) drug-susceptible active TB, and 2) multidrug-resistant TB, and two cohorts treated with isoniazid for latent TB infection (LTBI): 1) close contacts of persons with active TB, and 2) others newly diagnosed with LTBI. We evaluated four digital support strategies: two different medication monitors, synchronous video-observed therapy (VOT), and two-way short message service (SMS). Comparators were standard directly observed treatment for active TB and self-administered treatment for LTBI. Projected outcomes included costs (2016 US dollars), plus active TB cases and disability-adjusted life years averted among persons with LTBI.

For individuals with active TB, medication monitors and VOT are projected to lead to substantial (up to 58%) cost savings, in addition to alleviating inconvenience and cost to patients of supervised treatment visits. For LTBI treatment, SMS and medication monitors are projected to be the most cost-effective interventions. However, all projections are limited by the scarcity of published estimates of clinical effect for the digital technologies.

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Introduction

Tuberculosis burden and treatment challenges

Approximately one quarter of the world's population is estimated to have latent tuberculosis infection (LTBI) [1, 2], and each year, about 10 million individuals develop active tuberculosis (TB) [3, 4]. Despite the success of some strategies to reduce the global TB burden [5], TB remains a leading cause of mortality worldwide, causing an estimated 1.7 million deaths in 2016. Implementation challenges impede the success of directly observed treatment (DOT), as TB treatment is labour intensive for both patients and healthcare providers, requiring rigorous commitment from all to achieve good adherence and treatment success [6]. An effective DOT programme allows early detection and mitigation of suboptimal adherence, which otherwise leads to poorer patient outcomes, including acquired drug resistance [7] and increased costs for both the health system and patient. The latest global treatment success rates reported in 2016 were 83% among new and relapse TB patients, and 54% among persons with multidrug-resistant (MDR) TB (resistance to rifampicin and isoniazid) [4].

The World Health Organization (WHO) End TB Strategy aims to halt the TB epidemic by 2035. Beyond better adherence to treatment for active TB, this strategy also calls for improved detection and management of LTBI in countries with high and low TB burdens [8–10]. Obstacles to the uptake and completion of LTBI therapy include the need for testing and medical evaluation, treatment length and risks, and the necessity of follow-up visits with care providers [11, 12]. LTBI treatment is generally self-administered without supervision; consequently, adherence is inconsistent. A meta-analysis published in 2016 estimated that only 62% of persons starting preventive therapy completed treatment [11]. Only 13% of eligible contacts aged <5 years and 42% of people newly enrolled in HIV care were estimated to have started preventive treatment for LTBI in 2016, well below the target of ⩾90% envisaged for these subpopulations by the End TB Strategy for 2025 [4, 13]. Measures to improve treatment coverage and completion could increase the contribution of preventive therapy to reduce global TB incidence in the coming years.

Adherence support

Digital technologies have been evaluated extensively and used successfully to improve outcomes in HIV and other chronic diseases. They have been associated with improved adherence to treatment, with some initial evidence in the TB context [14–17]. The WHO guidelines on the management of LTBI recommend monitoring treatment using digital technologies [8] to further patient-centred care and support, key elements of the TB elimination framework [9]. Indeed, in 2016, WHO's Global Consultation on the Programmatic Management of LTBI called for digital technologies to be used in managing and treating LTBI [18], and in 2017 the Global TB Programme of the WHO released its first evidence-based recommendations on the use of digital technologies in support of TB treatment administration and adherence [19]. These guidelines acknowledged that further evidence is needed to understand the feasibility of implementing digital health technologies, and to measure the impact they could have on TB prevention and care [20–22]. In particular, evidence of the clinical impact of these interventions remains limited to date [17].

Published evaluations of digital health interventions in active TB and LTBI care have provided limited information about cost [23, 24]. Each digital health technology may entail substantial investment in hardware, software and/or infrastructure. Given the scarce funds for TB prevention and care, such costs must be considered alongside any anticipated gains in health outcomes. In this study, we used decision analysis models to begin to explore the costs and potential clinical impacts of the widely available and scalable technologies that are currently best positioned to replace in-person treatment observation either for active TB and/or to support treatment for LTBI that is currently self-administered. The technologies considered included video-observed therapy (VOT), electronic medication monitors and two-way text messaging (short message service; SMS). We considered their use in Brazil, a high TB burden setting with widespread access to smartphones and telephone network/internet coverage.

Methods

General description of models

For active TB disease, a decision analysis model was developed to simulate cohorts of 35-year-old adults (both sexes) who initiate TB treatment in Brazil. Patients were assumed to have either drug-susceptible TB (model 1) or MDR-TB (model 2). The simulation began at treatment initiation and allowed for two rounds of treatment if needed, representing a time horizon of 2–4 years. Two digital health interventions, VOT and medication monitors, were compared against standard DOT for treatment support of drug-susceptible TB and MDR-TB. We did not consider SMS support of active TB treatment, for reasons detailed later.

For LTBI, a decision analysis model simulated two cohorts of 35-year-old adults (both sexes) diagnosed with LTBI in Brazil. One cohort was comprised of individuals diagnosed with LTBI who were close contacts of drug-sensitive active TB cases. The other cohort consisted of members of the general population diagnosed with LTBI. Simulations began at treatment initiation and lasted 20 years. 9 months of daily isoniazid, supported by SMS, VOT or medication monitors, were compared with self-administered treatment (SAT), the standard of care for LTBI.

In all models, outcomes included disability-adjusted life years (DALYs) and costs for each strategy. For the LTBI cohorts, future incident TB cases were also projected.

Costs were expressed in 2016 US dollars (USD) and were projected from both the health system and societal perspectives. Where appropriate, cost-effectiveness was evaluated using incremental cost-effectiveness ratios. Models were developed using TreeAge Pro 2016 software (TreeAge Software Inc., Williamstown, MA, USA). Simplified schemas of the decision analysis models are included in the supplementary material.

Study setting
Brazil is a high TB burden country: in 2016 it had an estimated incidence of 87 000 TB cases (95% CI 74 000–100 000) at a rate of 42 cases per 100 000 population [4]. It has a comprehensive disease database, the Notification of Injury Information System (Sistema de Informação de Agravos de Notificação (SINAN); http://portalsinan.saude.gov.br), providing up-to-date clinical and TB programme data. This setting was chosen in part because of Brazil's high mobile-broadband penetration; in 2015 it had an 88% penetration, and was ranked fourth globally in active internet users [25].

Digital interventions
Digital health interventions were selected on the basis of a recent systematic review of digital technologies for TB [17]. The following sections give summaries of the strategies included. Table 1 provides more operational details and summarises the effect estimates for all digital interventions considered.

Medication monitors
Two medication monitor strategies were considered for treatment support for both active and latent TB: Wisepill (Wisepill Technologies, Somerset West, South Africa) and 99DOTS (an open-source toolkit). A randomised trial of treatment support for active TB in China reported that patients using medication monitors had 0.58 (95% CI 0.42–0.79) times the number of patient-months with 20% or more missed doses as those on standard care [33]. However, an impact on clinical outcomes was not demonstrated. In the primary analysis, we therefore made the conservative assumption that for active TB, medication monitors would yield treatment outcomes comparable to standard care with direct observation. There are no randomised studies evaluating medication monitors in LTBI care. Thus, in the LTBI model, we assumed that medication monitors would lead to better adherence than SAT in a context where support for LTBI treatment is very limited. We derived estimates of effect from the same trial in China [33]. A relative risk of 1.18 (95% CI 1.08–1.26) for treatment completion was calculated using published data from the Chinese trial (see supplementary material for detailed calculations).

Video-observed therapy
VOT was considered for treatment support for both active and latent TB. The VOT intervention was adapted from an observational study of active TB treatment support in New York City (USA) in 2014 [31]. The New York City study reported adherence with VOT of 95% of doses, compared to 91% for in-person DOT (p<0.01). In our active TB model, we thus assumed that treatment success rates using VOT for active TB were equivalent to those for in-person DOT. There are no published trials or other studies of VOT performed to monitor LTBI treatment. We assumed that VOT was likely to improve adherence to LTBI treatment relative to SAT. Thus, we assumed that the effect of VOT for LTBI would be equivalent to that of medication monitors.

SMS
Because randomised studies have suggested that SMS is not well suited to active TB care, we did not model this intervention in the context of active TB [35]. The two-way SMS intervention for LTBI was adapted from a study from British Columbia, Canada [32]. LTBI is usually treated using SAT, as is the case for HIV. We relied on the largest published randomised trial of two-way SMS for HIV treatment in Kenya (538 participants) [34], and assumed that the effect of two-way SMS on treatment completion was similar for LTBI and HIV. Again, extrapolating from the Kenyan trial, we assumed that SMS was likely to improve treatment support and completion in a context where existing support for LTBI treatment is very limited.

TABLE 1 Details of digital support interventions for treatment of active tuberculosis (TB) and latent TB infection (LTBI)

Digital technologies	Operational details	Estimate of effect	
		Active TB[#]	LTBI
MM: Wisepill	Small device attached to standard pill dispenser When opened, device communicates with web-based application by SMS Device sends SMS to patient and HCW when daily dose is missed One-way texting: no response is required of patient [26–28]	Assumed effect was equivalent to DOT/standard of care	Assumed effect was equivalent to that of MM in trials of active TB[¶]
MM: 99DOTS	Taking pills from blister pack daily reveals random toll-free numbers Any call from a registered patient number is marked as a dose taken When patients call, they hear "thank you" Automatic alerts to patients and HCW of missed doses pen-source information technology system [29, 30]	Assumed effect was equivalent to DOT/standard of care	Assumed effect was equivalent to that of MM in trials of active TB[¶]
VOT	Smartphone loaned to patients without one Pre-arranged schedule for real-time (synchronous) daily VOT calls with HCW Patient shows and names pills, then swallows them Patient asked about adverse reactions Missed appointments followed up first by phone calls, then by home visits [31]	Assumed effect was equivalent to DOT/standard of care	Assumed effect was equivalent to that of MM in trials of active TB[¶]
Two-way SMS	Weekly SMS "check-ins" sent from central computer at clinic Patients asked to respond within 24 h First instance of non-response: follow-up SMS Second instance of non-response: phone call [32]	Not estimated	Assumed effect was equivalent to that of two-way SMS in trials of HIV[+]

MM: medication monitor; VOT: video-observed therapy; SMS: short message service; HCW: healthcare worker; DOT: directly observed treatment. [#]: routine in-person DOT visits were replaced by digital technologies for active TB treatment supervision; [¶]: patients using digital interventions were 1.18 (95% CI 1.08–1.26) times more likely to complete treatment than those on self-administered treatment (derived from [33]); [+]: patients using digital intervention were 1.24 (95% CI 1.06–1.45) times more likely to complete treatment than those on self-administered treatment [34].

Data sources

Pathogenesis, natural history of TB, epidemiology and drug resistance data were taken from published literature, and are summarised in supplementary table S3. Treatment outcomes were derived from 2013–2014 country-specific data from the Brazilian national TB programme (supplementary table S1). For cost-utility analyses, a weight of 0.331 DALYs was attributed to active TB (95% CI 0.224–0.454) [36], and a weight of 0 DALYs was attributed to LTBI, as individuals with LTBI are asymptomatic (supplementary table S3). Further description of the DALY calculations is provided in the supplementary material.

Costs

All costs were expressed in 2016 USD, using relevant exchange rates and published inflation indices for Brazil and for any other countries from which cost data were obtained (see supplementary material). Costs obtained from India and South Africa were normalised to the Brazilian per capita gross national income (GNI), by multiplying them by the number resulting from dividing Brazilian per capita GNI by Indian or South African per capita GNI for the relevant year. During the 20-year simulation of individuals with LTBI, all future costs and outcomes were discounted at an annual rate of 3%.

Digital technology costs

Technology costs included materials required to implement the interventions, such as phones, dispensers and envelopes. Start-up and follow-on operational costs for each technology, training costs and staff pay based on the time needed to complete an activity, including steps taken to follow up with patients reporting problems or demonstrating suboptimal adherence, were also incorporated. Table 2 serves as an example of the types of cost components included for the SMS intervention and is shown as a per person cost. Detailed cost breakdowns for all other interventions are shown in supplementary table S9.

Treatment-related health system costs

Health system costs included staff salaries for all DOT and other follow-up visits, costs of follow-up monitoring tests and drug costs. DOT visits were assumed to occur three times weekly, as recommended by Brazilian authorities [41], with other treatment doses self-administered. For re-treatment, diagnostic costs were also included. Hospitalisation and adverse event management costs were based on published estimates [42, 43] (supplementary tables S4–S7). Patient costs were classified as direct (out-of-pocket expenses related to medical visits) and indirect (time lost due to medical visits) (supplementary table S8). Table 3 summarises aggregate cost inputs used for standard treatment regimens for the different cohorts and for each of the intervention scenarios. These aggregate costs reflect the costs incurred by the health system and patient for diagnosis and treatment (varying depending on type of TB), plus any additional costs relevant to each of the specific digital technologies (as shown for SMS in table 2).

Scenario and sensitivity analyses

Due to the paucity of empirical data on clinical outcomes with the digital interventions, we considered several alternative scenarios to those already described. For active TB, we considered the possibility that medication monitors and VOT may actually improve TB treatment outcomes relative to DOT. In this scenario, we assumed that improved adherence as reported in China would lead to improved treatment success rates, and applied the ratio reported by LIU *et al.* [33] to unfavourable treatment outcomes (loss to follow-up, death and failure) in the medication monitor and VOT intervention arms of the model.

An alternative analysis for the LTBI cohorts focused only on cost differences between scenarios, setting the effect of all interventions to be equivalent to that used for medication monitors in the baseline analyses (*i.e.* relative risk of 1.18 for treatment completion, compared to SAT). Additionally, a threshold analysis was conducted for the LTBI cohort to identify the minimal efficacy required of the intervention in order for it to remain cost-effective when considering DALYs averted.

Probabilistic sensitivity analyses were used to generate 95% uncertainty ranges (UR; 2.5th to 97.5th percentiles) around point estimates for all projected outcomes. They were also used to further explore the potential cost-effectiveness of these technologies. Additional sensitivity analyses, including one-way

TABLE 2 Digital technology costs for treatment support using two-way short message service (SMS), per person with latent tuberculosis infection (LTBI), in 2016 USD[#]

	Item	Value	Reference or calculation
A	Server: cost of one server (3 servers needed, 1 server per 100 000 patients)	USD 2000	Personal communication[¶]
B	Server: start-up cost (per patient)[+]	USD 0.02	Calculated from A
C	Server: monthly server fees (unit cost)	USD 960	Personal communication[¶]
D	Server: monthly fee (per patient)[+]	USD 0.01	Calculated from C
E	Data and phone costs per patient per month	USD 0.21	[34, 37][§]
F	Number of messages per month (1 per week)	4.3	
G	Cost of a single SMS in Brazil	USD 0.02	[38]
H	Proportion of patients who respond to SMS with a problem	0.06	Assumption[f]
I	Proportion of patients who do not respond to first SMS	0.38	[11][##]
J	HCW time required to respond to patient who does not respond, *i.e.* time to send second SMS	1.5 min	[39]
K	HCW time required to respond to patient with problem	20 min	Assumption[¶¶]
L	Mean, weighted HCW time per patient	1.81 min	Calculated as (H×K)+(I×J)
M	TB nurse wage per min	USD 0.16	
N	Subtotal: treatment support cost	USD 0.29	Calculated as L×M
O	Mean, weighted message/phone costs associated with second SMS for patients who do not respond (to be added to all patients)	USD 0.01	Calculated as G×I
P	Mean nurse training cost (*pro rata* per LTBI case)	USD 3.35	Personal communication[¶]
Total	**Complete cost for 9 months of LTBI treatment support**	**USD 6.32**	Calculated as B+(9×(D+E+(F×G)))+N+O +P per person

HCW: healthcare worker; TB: tuberculosis. [#]: the aggregate cost does not include cost components related to diagnosis or treatment (see table 3). [¶]: Richard Lester (University of British Columbia, Vancouver, BC, Canada) from the WelTel trial [34]. [+]: Brazil has ~70 000 new active TB cases per year; assuming four contacts per case, we assumed that 280 000 contacts per year would receive treatment in 4745 TB clinics [40]. [§]: calculated as clinic cost/mean number of patients per clinic (WelTel)/36 months (length of WelTel trial). [f]: equivalent to total adverse event rates for LTBI. [##]: assumed from the reported global LTBI treatment completion rate, conditional on initiating treatment. [¶¶]: time on the phone is assumed to be equivalent to in-person adverse event consultation.

TABLE 3 Total input cost per person with tuberculosis (TB) or latent TB infection (LTBI) for diagnosis and treatment, by type of digital technology used for treatment support, in 2016 USD

	Treatment length months	Total costs incurred by health system					Total costs incurred by patient	
		Standard of care	VOT	MM: Wisepill	MM: 99DOTS	SMS	Standard of care	Digital technology
Drug-susceptible TB	6	845	505	368	340	NA	299	140
MDR-TB	18	10014	8879	8527	8494	NA	813	337
LTBI	9	53	397	91	61	59	148	148

Costs listed account for pre-diagnostic management, diagnosis, treatment and follow-up. VOT: video-observed therapy; MM: medication monitor; SMS: short message service; MDR: multidrug-resistant; NA: not applicable.

sensitivity analyses for key parameters used in each model and relevant tornado diagrams, are described in the supplementary material.

Results
Health system perspective
Drug-susceptible TB and MDR-TB cohorts
Assuming equivalent drug-susceptible TB treatment success rates with DOT and digital interventions, all interventions led to health systems cost savings relative to standard DOT, ranging from 39% to 58%. For the MDR-TB cohort, all digital interventions also led to health system cost savings, where treatment success rates were assumed to be equivalent to those with DOT. Relative to DOT, cost savings ranged from 11% to 15%. Further details are provided in table 4.

LTBI cohorts
Among close contacts with LTBI, SMS and the medication monitors were projected to be most cost-effective compared to SAT. The incremental cost of SMS was USD 5 per person, with a reduction in DALYs of 0.04 per person, and a 0.8% absolute decrease in future TB incidence over the 20-year simulation. The incremental cost of SMS was USD 123 per DALY averted, and USD 611 per TB case prevented. Both medication monitors and VOT averted 0.03 DALYs per person, and led to an absolute reduction in TB incidence of 0.6%. The 99DOTS medication monitor was the second most cost-effective intervention, with an incremental cost of USD 210 per DALY averted, and USD 1038 per TB case prevented. The Wisepill medication monitor had an incremental cost of USD 1178 per DALY averted, and USD 5836 per TB case prevented. VOT had an incremental cost of USD 9805 per DALY averted, and USD 48 551 per TB case prevented. Complete results are shown in table 5.

Among persons from the general population with LTBI, SMS was the most cost-effective intervention. SMS cost USD 1000 per DALY averted and USD 4483 per TB case prevented compared to SAT (table 5).

Societal perspective
Drug-susceptible TB and MDR-TB cohorts
Combining health system and patient costs, cost savings with digital technologies for the drug-susceptible TB cohort ranged from 43% to 56%, and from 15% to 18% for MDR-TB, relative to standard DOT. Estimated savings to patients were USD 168 for each drug-susceptible TB patient and USD 593 for each MDR patient. See table 4 for full details.

LTBI cohorts
In both LTBI cohorts, results from the societal perspective (table 5) were similar to those from the health system perspective. In close contacts, SMS was projected to be the most cost-effective and VOT the least. As expected, all interventions were less cost-effective in unselected persons with LTBI. The highest incremental cost-effectiveness ratios were for VOT, with estimated costs of USD 44 042 per DALY averted and USD 197 411 per TB case prevented.

Scenario and sensitivity analyses
In the additional analysis for the active TB cohort, where medication monitors and VOT were assumed to lead to better treatment outcomes than DOT, digital technologies were estimated to improve treatment success rates in the drug-susceptible TB cohort from 71% with DOT (95% UR 71–72%) to 83% (95% UR 79–87%), and to reduce DALYs accrued by 39%, from 3.2 (95% UR 3.1–3.3) to 1.9 (95% UR 1.6–2.4) per

TABLE 4 Projected costs of strategies using digital support for active tuberculosis (TB) treatment, in 2016 USD

Digital support strategy	Cost per person	Incremental savings *versus* DOT
Drug-susceptible TB cohort		
Health system perspective		
DOT	930 (876–1095)	Comparator
VOT	567 (529–660)	363 (302–490)
MM: Wisepill	423 (392–511)	507 (450–631)
MM: 99DOTS	394 (363–482)	536 (479–660)
Societal perspective		
DOT	1249 (903–3069)	Comparator
VOT	718 (572–1170)	531 (69–2320)
MM: Wisepill	574 (431–1032)	675 (217–2394)
MM: 99DOTS	545 (402–1003)	704 (249–2463)
MDR-TB cohort		
Health system perspective		
DOT	12 585 (12 395–13 184)	Comparator
VOT	11 177 (11 027–11 563)	1409 (1212–1826)
MM: Wisepill	10 754 (10 623–11 128)	1831 (1648–2235)
MM: 99DOTS	10 715 (10 584–11 089)	1870 (1686–2274)
Societal perspective		
DOT	13 650 (12 537–19 923)	Comparator
VOT	11 648 (11 224–12 769)	2002 (371–8095)
MM: Wisepill	11 225 (10 817–12 358)	2425 (789–8195)
MM: 99DOTS	11 186 (10 779–12 319)	2463 (828–8234)

Data are presented as cost or savings with 95% uncertainty ranges. DOT: directly observed treatment; VOT: video-observed therapy; MM: medication monitor; MDR: multidrug-resistant.

patient. With this scenario, societal cost savings relative to DOT were USD 543 with VOT, USD 687 with the Wisepill medication monitor and USD 716 with the 99DOTS medication monitor. For the MDR-TB cohort, these technologies were projected to improve treatment success rates from 59% with standard DOT (95% UR 57–62%) to 75% (95% UR 69–80%), and reduce DALYs by 35%, from 5.2 (95% UR 4.8–5.6) to 3.4 (95% UR 2.9–4.2) per patient.

The additional scenario analysis for our LTBI model, which set effectiveness equal for all digital interventions so as to compare their costs, yielded results consistent with our primary findings. In this analysis, two-way SMS and 99DOTS medication monitor remained the most cost-effective interventions: the incremental cost (95% UR) of SMS was USD 164 (USD 29 saving to USD 362 cost) per DALY averted, and USD 814 (USD 137 saving to USD 1781 cost) per TB case prevented.

In the active TB cohorts, the probabilistic sensitivity analysis suggested that medication monitors and VOT were likely to be cost saving within all model parameter ranges considered. For the LTBI models, SMS, 99DOTS medication monitor and Wisepill medication monitor were cost-effective (using USD 8650, the mean per capita gross domestic product in Brazil, as the willingness-to-pay threshold) relative to SAT in 100% of simulations among close contacts of persons with LTBI. Among members of the general population newly diagnosed with LTBI, these technologies were cost-effective in more than 90% of simulations, using the same willingness-to-pay threshold. VOT was cost-effective in only 60% of simulations in the cohort of close contacts, and was not cost-effective among members of the general population with LTBI.

Discussion

This analysis is the first to examine the potential cost and impact of digital technologies as applied under programme conditions in a high TB burden country. It provides preliminary insights into the potential impact and cost of several approaches to TB treatment support in this context. For active TB, we estimated substantial cost savings with VOT and medication monitors, including savings to patients and their families, compared to conventional in-person DOT. Compared to SAT for LTBI treatment, two-way SMS and medication monitors are projected to be the most cost-effective technologies, especially for close contacts with LTBI; they are less cost-effective for others with LTBI. Until VOT becomes cheaper, it will probably be substantially less cost-effective for supporting LTBI treatment as currently delivered in Brazil and similar settings, despite improvements in rates of treatment completion. Although Brazil was the focus

TABLE 5 Projected cost-effectiveness of strategies using digital support for latent tuberculosis infection (LTBI) treatment, in 2016 USD

Digital support strategy	Cost per person	Incremental cost *versus* SAT[#]	DALYs accrued	Incremental cost per DALY averted *versus* SAT[#]	TB incidence %	Incremental cost per TB case prevented *versus* SAT[#]
LTBI cohort: close contacts						
Health system perspective						
SAT	60 (50–103)		0.1 (0.07–0.24)		2.0 (1.5–4.6)	
MM: Wisepill	96 (84–136)	36 (29–38)	0.07 (0.05–0.17)	1178 (375–2171)	1.4 (1.1–3.4)	5836 (1875–10704)
MM: 99DOTS	67 (55–107)	7 (−7–8)	0.07 (0.05–0.17)	210 (−10–445)	1.4 (1.1–3.4)	1038 (−40–2195)
VOT	356 (314–421)	296 (246–340)	0.07 (0.05–0.17)	9805 (3658–17596)	1.4 (1.1–3.4)	48551 (18744–83722)
SMS	65 (53–105)	5 (−6–8)	0.06 (0.03–0.16)	123 (−57–311)	1.2 (0.8–3.1)	611 (−273–1556)
Societal perspective						
SAT	181 (79–477)		0.1 (0.07–0.24)		2.0 (1.5–4.6)	
MM: Wisepill	226 (114–546)	45 (24–71)	0.07 (0.05–0.17)	1495 (389–2801)	1.4 (1.1–3.4)	7404 (1816–13477)
MM: 99DOTS	197 (85–517)	16 (−5–42)	0.07 (0.05–0.17)	527 (−100–1356)	1.4 (1.1–3.4)	2608 (−564–6414)
VOT	486 (358–806)	305 (250–355)	0.07 (0.05–0.17)	10122 (3730–17547)	1.4 (1.1–3.4)	50119 (18756–86092)
SMS	198 (82–531)	17 (−13–58)	0.06 (0.03–0.16)	440 (−168–1223)	1.2 (0.8–3.1)	2180 (−819–5837)
LTBI cohort: general population newly diagnosed with LTBI						
Health system perspective						
SAT	50 (39–83)		0.030 (0.030–0.055)		0.7 (0.6–1.2)	
MM: Wisepill	89 (76–124)	39 (37–41)	0.023 (0.022–0.044)	5520 (2722–7818)	0.5 (0.5–1.0)	24745 (12327–35197)
MM: 99DOTS	60 (46–94)	10 (8–12)	0.023 (0.022–0.044)	1370 (639–1849)	0.5 (0.5–1.0)	6180 (2893–8273)
VOT	349 (303–412)	299 (251–346)	0.023 (0.022–0.044)	42481 (20534–60702)	0.5 (0.5–1.0)	190415 (92588–271118)
SMS	59 (45–95)	9 (7–13)	0.021 (0.017–0.042)	1000 (383–1479)	0.5 (0.3–0.9)	4483 (1755–6632)
Societal perspective						
SAT	167 (63–445)		0.030 (0.030–0.055)		0.7 (0.6–1.2)	
MM: Wisepill	216 (101–519)	49 (38–76)	0.023 (0.022–0.044)	7081 (3080–10460)	0.5 (0.5–1.0)	31740 (14115–45303)
MM: 99DOTS	187 (72–490)	20 (8–47)	0.023 (0.022–0.044)	2931 (804–5508)	0.5 (0.5–1.0)	13136 (3656–24628)
VOT	477 (342–783)	310 (256–362)	0.023 (0.022–0.044)	44042 (20986–62452)	0.5 (0.5–1.0)	197411 (96567–278873)
SMS	190 (72–507)	23 (7–68)	0.021 (0.017–0.042)	2561 (535–5166)	0.5 (0.3–0.9)	11479 (2407–22869)

Data are presented with 95% uncertainty rangesAQcon. Outcomes are projected over a 20-year time horizon, with 3% discounting. SAT: self-administered treatment; DALY: disability-adjusted life year; TB: tuberculosis; MM: medication monitor; VOT: video-observed therapy; SMS: short message service. [#]: negative values indicate cost saving.

of our analysis, these results could potentially be relevant to other settings (recognising that treatment practices will vary, *e.g.* in many settings, 6 months of isoniazid is the norm when LTBI is treated).

Our analysis highlights the paucity of published data on the clinical impact of digital interventions for TB. Few randomised trials exist and many of the published results are from studies in very specific treatment settings, *e.g.* for active TB treatment in New York and China and HIV treatment in Kenya; these may not be generalisable to other populations and clinical settings including active TB and LTBI treatment in Brazil. Consequently, our analyses relied on estimates of clinical effectiveness that were often extrapolated from short-term data regarding adherence. Moreover, we based several estimates on the Chinese study of medication monitors where the control arm involved a mix of DOT and SAT, which could overestimate the benefit of medication monitors when compared with true DOT. We investigated the impact of uncertainty in our parameter estimates through extensive sensitivity analyses. However, if subsequent field trials suggest poorer clinical outcomes for a given digital support technology *versus* conventional DOT, that technology is unlikely to be implemented further in active TB treatment, regardless of associated cost savings.

Published data on the costs of digital interventions are also scarce and sometimes out-dated. Particularly in low- and middle-income countries, technology-related costs can change rapidly due to improvements in infrastructure, such as internet connectivity. Whenever possible, we contacted study authors and manufacturers to obtain the best available cost estimates, and accounted for variability and uncertainty in sensitivity analyses. It should be noted that technology costs considered in this study do not include initial technology development and upstream support as they are beyond the scope of our analyses. There are also costs inherent to implementing technologies at large scale (beyond costs of training, hardware and software), which are difficult to capture.

In our study, we assumed that costs and outcomes for standard care of active TB reflected direct observation. This assumption almost certainly overestimated the total number and cost of DOT visits that in fact occur under programme conditions. We did not have data for the precise number of DOT visits that actually take place. We may also have overestimated use of Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) for TB diagnosis, which could lead to some overestimation of diagnostic costs for persons with LTBI who subsequently develop active TB. Furthermore, our models assumed 100% adoption of the digital technologies. Under programme conditions, uptake is likely to be less, a point again explored *via* varying efficacy estimates in sensitivity analysis. Additional analyses involving variable uptake as well as combinations of these technologies, or only partial replacement of DOT in active TB, could provide further insight.

In Brazil, the estimated costs of TB for the health system and for patients and families are substantially lower than in a higher-income setting like the USA. For example, CASTRO *et al.* [44] estimated health system costs of USD 17 000 for each case of drug-susceptible TB, plus additional costs to patients and families of USD 3000 and lost income of USD 374 000 for each patient who dies prematurely from drug-susceptible TB. Hence, to the extent that digital technologies reduce health system costs, and might potentially improve treatment outcomes in LTBI, resulting savings could be greater in higher-income settings. In the case of LTBI, where we assumed improved treatment adherence with the digital technologies, and hence a lower risk of future reactivation, we did not consider societal cost savings related to reductions in subsequent death and long-term disability. However, we did estimate DALYs averted.

In the future, digital support strategies may not only serve to improve adherence to TB and LTBI treatment, but may also improve monitoring of adverse events, a particular concern with SAT. SMS and VOT could allow patients to report potential adverse reactions and other concerns in a more timely manner, potentially improving outcomes and reducing costs. Our models could not account for this additional advantage, due to the lack of published evidence describing it. As additional trial data become available, this will be a worthwhile avenue of inquiry. More generally, digital technologies offer the possibility of detecting adherence gaps, in a less intrusive and expensive manner than traditional DOT. Any such gaps must then be addressed by tailored, patient-centred approaches, which could include digital and/or in-person interactions.

As in other health domains, digital technologies can potentially replace or enhance existing treatment models [45, 46], but such a paradigm shift comes with challenges in development, design, implementation, maintenance, accessibility and acceptability [47, 48]. For example, patients theoretically could "cheat" medication monitor systems by opening dispensers or blister packs without ingesting medication; this would falsely be recorded as good adherence [26, 33]. Although not completely foolproof, VOT maintains direct observation of medication ingestion, but may be perceived as intrusive by some patients [49]. When adopting digital technologies in the TB context, we can draw lessons from other fields where solutions were tailored to the perspectives of patients and providers to enhance feasibility [50, 51].

Digital support technologies may be more cost-effective with intermittent isoniazid treatment, or with newer and shorter LTBI medication regimens, such as the 12-dose weekly isoniazid/rifapentine combination. This was initially administered under direct, in-person observation [52]; however, a recent study reported no benefit for one-way SMS reminders added to standard SAT for this regimen [53]. Increasing global availability of these regimens justifies further evaluation of the cost-effectiveness of two-way SMS, medication monitors and VOT to support shorter-course LTBI treatment. It is also conceivable that with higher adherence to the self-administered shorter-course regimens, digital technologies could in fact provide less benefit in this regard; this possibility also warrants further evaluation.

Conclusion

Although DOT has long been held up as the paragon for active TB treatment support, it is not always possible to implement optimally. Our analysis shows that digital technologies may reduce costs and improve treatment support for persons treated for active TB. However, more evidence of their value is needed, especially in the context of TB care. Furthermore, this analysis again emphasises that LTBI treatment and treatment support should focus on persons at higher risk of developing active TB. By helping to improve the management of LTBI, digital technologies could contribute to reducing TB incidence and meeting the goals of the WHO End TB Strategy.

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