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Themed Section: Remote Patient Monitoring

## Cost and Cost-Effectiveness of a Digital Adherence Technology for Tuberculosis Treatment Support in Uganda



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### ABSTRACT

**Objectives:** Digital adherence technologies like 99DOTS are increasingly considered as an alternative to directly observed therapy for tuberculosis (TB) treatment supervision. We evaluated the cost and cost-effectiveness of 99DOTS in a high-TB-burden setting.

**Methods:** We assessed the costs of implementing 99DOTS in Uganda through a pragmatic, stepped-wedge randomized trial. We measured costs from the health system perspective at 5 of 18 study facilities. Self-reported service activity time data were used to assess activity-based service costs; other costs were captured from budgets and key informant discussions using standardized forms. We estimated costs and effectiveness considering the 8-month study period (“trial specific”) and using a 5-year time horizon (“extended activities”), the latter including a “marginal clinic” expansion scenario that ignored above-site implementation costs. Cost-effectiveness was assessed as cost per patient successfully completing treatment, using Monte Carlo simulation, cost-effectiveness acceptability curves, and sensitivity analyses to evaluate uncertainty and robustness of results.

**Results:** The total cost of implementing 99DOTS in the “trial-specific” scenario was \$99 554 across 18 clinics (range \$3771–\$6238 per clinic). The cost per treatment success in the “trial-specific” scenario was \$355 (range \$229–\$394), falling to \$59 (range \$50–\$70) assuming “extended activities,” and \$49 (range \$42–\$57) in the “marginal clinic” scenario. The incremental cost-effectiveness of 99DOTS in the “extended-activity” scenario was \$355 per incremental treatment success.

**Conclusions:** Costs and cost-effectiveness of 99DOTS were influenced by the degree to which infrastructure is scaled over time. If sustained and scaled up, 99DOTS can be a cost-effective option for TB treatment adherence support in high-TB-burden settings like Uganda.

**Keywords:** 99DOTS, cost analysis, cost-effectiveness analysis, digital adherence technology, tuberculosis.

VALUE HEALTH. 2022; 25(6):924–930

### Introduction

Despite being a treatable disease, tuberculosis (TB) remains one of the top 10 causes of death globally, with an estimated 1.5 million deaths in 2020.<sup>1</sup> An important contributing factor to the global TB disease burden is insufficient treatment adherence. Current treatment typically requires at least 6 months of daily, directly observed therapy (DOT).<sup>2,3</sup> The sustainability of DOT has been questioned due to its nonpatient-centered approach and resource-intensive nature (eg, high workload for clinical staff).<sup>4–6</sup> As such, in many high-TB-burden settings, 15% or more of patients with TB do not complete treatment. Incomplete treatment adherence can lead to relapse, worsened clinical outcomes, development of drug resistance, and ongoing transmission, all of which can adversely affect the health and economic wellbeing of patients, caregivers, and health systems.<sup>7–9</sup>

Digital adherence technologies (DATs) are an emerging strategy for monitoring (and thus improving) TB treatment adherence. Medication Event Monitoring Systems, video-observed therapy, and short message service (SMS)-based “smart lids” for pillboxes are DAT platforms that have been shown to improve TB treatment success,<sup>9–11</sup> but their infrastructure requirements (eg, network connection, installation of peripheral monitoring systems in homes) and high maintenance costs are potential hurdles to scalability and sustainability. 99DOTS (Everwell Health Solutions, India) is a promising low-cost, minimal-infrastructure alternative to traditional DATs.<sup>12</sup> The core component of 99DOTS is a specially designed medication blister pack that reveals a unique toll-free phone number when patients remove pills.<sup>12–15</sup> To confirm their dose, patients call the number, and an automated system records their dose confirmation in real-time through an online dashboard. Health workers access adherence data from the dashboard, using

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those data to identify patients struggling to adhere to treatment. Additional support is provided to those patients through targeted SMS messaging, phone calls, and home visits.<sup>12,14</sup>

Uganda has an estimated 90 000 new cases of TB annually.<sup>1</sup> TB treatment coverage and adherence is suboptimal with less than 20% of TB clinics properly implementing DOT<sup>16</sup> and fewer than 75% of patients successfully completing treatment.<sup>1</sup> A recent real-world randomized trial in Uganda (DOT to DAT trial)<sup>14</sup> demonstrated that 99DOTS can (1) be iteratively adapted to meet local user needs<sup>17</sup> and (2) effectively facilitate treatment adherence and improve treatment success.<sup>15</sup> Nevertheless, evidence on the cost and cost-effectiveness of this approach remain limited. Therefore, we performed an empiric costing and cost-effectiveness analysis of 99DOTS as part of the DOT to DAT trial in Uganda.

## Methods

### Overview

DOT to DAT was a pragmatic stepped-wedge randomized trial evaluating the impact of operating 99DOTS at 18 health facilities (5 referral hospitals, 10 general hospitals, 3 district health centers) in Western, Central, and Eastern Uganda with National TB and Leprosy Program-affiliated TB treatment units between December 2018 and July 2019.<sup>14,15</sup> All clinics managed at least 10 patients with TB per month and had treatment success rates below 80% before the trial; see Appendix 1 and Appendix Table 1.3 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002> for detailed clinic characteristics.<sup>14,15</sup> Using a stepped-wedge design, 3 clinics were randomly chosen to introduce the 99DOTS intervention each month, with the first month post-transition serving as a “buffer” period.

### Data Collection

#### Costs

We purposively selected 5 clinics that represented a range of characteristics (distance from Kampala, annual volume of patients treated for TB, and size of catchment population [represented by tier of healthcare system]) to collect resource-use and cost data (bottom-up and top-down) for all implementation and operational processes for 99DOTS.<sup>18</sup> Resources were categorized into 5 groups: staff, equipment, supplies, building, and overheads. Annual building (rent and furniture) and overhead (utilities) costs were collected from each clinic's budgets using a standardized form. Equipment and supply costs were collected by reviewing procurement logs, receipts, and purchase orders at each clinic for goods related to 99DOTS. Staff costs were based on actual salaries collected from clinics or official pay scales published by the Ministry of Public Service.<sup>19</sup>

99DOTS technology costs were tracked separately and categorized as technology support/hosting and implementation costs. Technology support/hosting fees were based on quotes and standardized discussions from the implementing partner that included costs to access and use the 99DOTS system platform. Implementation costs, inclusive of the packet design process and production, were collected through specially designed surveys to log activity-based resources used for 99DOTS intervention implementation activities such as training, while excluding costs associated with research activities (eg, patient consent).

#### Allocation of resources

At the 5 selected clinics, we conducted a service time assessment (STA) study using activity-based self-report time forms to assess human resource requirements for 99DOTS. STA studies

were performed over 1 week per clinic during a routine visit. Consenting healthcare workers involved in TB-related services provided self-reported information on the frequency and duration of activities (TB, non-TB, and 99DOTS specific) conducted on each working day during the week using a standardized form. The form was designed to capture the duration of each activity and the number of patient interactions in 30-minute time blocks. Using the STA study data, we ascertained and categorized per-patient and per-activity times required for each component of 99DOTS service delivery.

In addition to STA studies, we also reviewed an activity log kept by the 99DOTS system database that tracks frequency and types of patient interactions with the 99DOTS system (eg, calls to the toll-free line). These data were combined with self-reported STA data to estimate the total time apportioned to 99DOTS. These time estimates were multiplied by unit salary estimates to calculate per-patient human resource costs. Further details on STA data and analysis are available in Appendix 1 and Appendix Tables 1.1 and 1.2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>.

### Resource Valuation

To estimate the value of equipment, implementation expenses, and other fixed costs associated with the 99DOTS intervention, we first assessed total costs for the entire trial period and, where applicable, further annuitized these estimates using a 3% discount rate over their expected life-years. These costs were then assessed as per-clinic total and annual costs and then divided by the number of patients managed with 99DOTS to compute per-patient costs. For 99DOTS related supplies (airtime, printing, packaging, and shipping of envelopes), the implementing partner charged a fixed per-patient cost of \$12 per 6-month TB treatment, pro-rated based on the amount of time a patient was managed with 99DOTS (eg, only \$2 would be assessed for a patient who was lost to follow-up after 1 month). A 99DOTS technology/hosting fee was assessed as a fixed monthly rate that was split evenly across study clinics, plus a per-patient cost that was applied directly to each patient managed. Remaining costs (building, overhead, staff) were estimated using activity- and patient-based STA data. All costs were estimated from the health system perspective and inflated to 2019 currency using the World Bank's gross domestic product deflator for Uganda and converted to US dollars (USD) using the World Bank's 2019 exchange rates (1 USD = 3704 UGX).<sup>20,21</sup> Detailed information on the resource-use valuation can be found in Appendix 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>.

### Analytical Scenarios

99DOTS-based treatment support costs were calculated under 3 scenarios. First, we assessed the “trial-specific” costs, limiting the scope of analysis to the 8-month trial period—thus implicitly assuming that intervention activities would cease after the trial and no resources were shareable beyond the trial period. Second, we considered an “extended activities” scenario, in which we assumed that 99DOTS activities would be sustained for a 5-year time horizon in the study clinics without additional capital costs during this period (eg, initial training, new capital assets). As such, we annuitized fixed and implementation costs over this time period and report corresponding annual costs. Third, we projected a “marginal clinic” scenario, using the same 5-year time horizon but estimating the cost of introducing 99DOTS into a new clinic, assuming that the 99DOTS system infrastructure established for the trial could be shared with that clinic (thus reducing per-clinic fixed costs). In this scenario, incremental implementation costs

would only include variable costs relevant for the implementation process (such as initial and follow-up training at that clinic and establishment of clinic-level systems to manage patients).

### Cost Analyses

Cost outcomes of interest were the total cost of 99DOTS implementation and service delivery for 1 clinic and for all 18 study clinics, per-patient costs of the 99DOTS intervention, and cost per patient successfully completing TB treatment. To estimate the total costs of 99DOTS across all 18 study clinics (given that most of the measured above-site implementation costs applied to all 18 clinics), we used a combination of cost estimates from the 5 selected costing clinics and 99DOTS operational data available for all 18 clinics, as detailed in [Appendix Figure 1.1](https://doi.org/10.1016/j.jval.2021.12.002) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>.

Total and unit costs of performing 99DOTS-related activities were initially assessed for the 5 selected clinics using self-reported STA data. These cost estimates were then mapped to each 99DOTS activity as logged across all 18 study clinics. Total 99DOTS service delivery costs were calculated as the product sum of the empiric activity-based unit cost estimates and the frequency of each activity performed across the 18 study clinics. Total equipment (capital) and implementation costs for the study were estimated based on mean total cost estimates from the empiric costing clinics, which were then mapped to noncosting clinics based on study operations (eg, training and clinic visits and central 99DOTS service use logs; see [Appendix Fig. 1](https://doi.org/10.1016/j.jval.2021.12.002) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>). Where available, cost and resource-use data unique to each clinic were used (eg, logs of 99DOTS technology support and procurement of supplies).

For the “extended activities” scenario, we performed 1-way deterministic sensitivity analyses to explore key drivers of our primary cost estimates. Results of these analyses were then used to estimate the potential range of costs that might be experienced in different contexts as defined by annual service volume, 99DOTS monthly server costs, estimated life-years of equipment, and the discount rate.

### Cost-Effectiveness Analysis

The primary cost-effectiveness outcome was the incremental cost per additional patient with TB successfully completing treatment using 99DOTS. The 99DOTS intervention costs were assessed as incremental costs to the status quo (ie, assuming no difference in TB treatment costs between the 2 arms of the trial beyond 99DOTS-specific expenses). Successful treatment completion was defined according to the TB treatment register at each clinic. Effectiveness data were available from all 18 clinics and were based on the per-protocol patient population, defined as patients enrolled on 99DOTS within 1 month of treatment initiation, with treatment initiation occurring while the facility was in the intervention phase of the study.<sup>15</sup>

To calculate the incremental cost-effectiveness ratio and cost-effectiveness outcomes in the “extended activities” and “marginal clinic” scenarios, we modeled outcomes and uncertainties in a hypothetical setting using the empiric cost and effectiveness data in the DOT to DAT trial. We constructed beta distributions around the minimum and maximum observed values for each cost category (eg, average supply cost per patient) and effectiveness outcome (eg, percent treatment completion on 99DOTS), with the mode set at the weighted mean. In each iteration, the incremental cost of 99DOTS was estimated as the total cost per 100 patients using 99DOTS in the “extended activities” scenario. The incremental effectiveness outcome was the number of additional

treatment successes per 100 patients on 99DOTS. A full list of parameters and values is available in [Appendix Table 2.1](https://doi.org/10.1016/j.jval.2021.12.002) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>.

We ran a Monte Carlo simulation with 10 000 iterations, pulling values from these distributions to build unique estimates of cost per patient, cost per treatment success, total cost of 99DOTS, service volume, and number of treatment successes—for both the intervention and control arms. Each iteration reflects outcomes for a single modeled clinic. From these modeled clinics, we estimated the mean values for total cost, cost per patient, and cost per treatment success, with 95% uncertainty ranges (URs) representing the 2.5th and 97.5th percentile of observed values for each outcome. We constructed cost-effectiveness acceptability curves and a cost-effectiveness plane to demonstrate the likelihood of the cost-effectiveness of the 99DOTS intervention at various willingness-to-pay thresholds. All analyses were performed using Stata version 15.1 and R version 4.0.2.

### Ethics Statement

Institutional review boards at the University of California San Francisco and Makerere University approved the study. All staff who participated in STA studies provided an informed consent.

## Results

### Cost Estimates

The total annual cost of implementing 99DOTS across 18 clinics was estimated as \$99 554 in the “trial-specific” scenario, \$86 492 in the “extended activities” scenario, and \$71 058 in the “marginal clinic” scenario ([Table 1](https://doi.org/10.1016/j.jval.2021.12.002)). The average annual per-clinic cost was \$5268 (95% observed range [UR] \$3771–\$6238) in the “trial-specific” scenario.

The average cost per patient supported by the 99DOTS platform was \$303 (observed range \$220–\$2119) in the “trial-specific” scenario, but fell to \$51 (95% UR \$44–\$60) assuming “extended activities” for 5 years and to \$42 (95% UR \$37–\$49) in the “marginal clinic” scenario assuming existing infrastructure in place ([Table 2](https://doi.org/10.1016/j.jval.2021.12.002)). The main per-patient cost components of 99DOTS in the “extended activities” scenario were technology support (45.0%), implementation (21.8%), supplies (21.0%), and equipment (7.8%). See [Appendix 3](https://doi.org/10.1016/j.jval.2021.12.002) and [Appendix Table 3.1](https://doi.org/10.1016/j.jval.2021.12.002) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002> for a breakdown of each cost component.

The deterministic sensitivity analysis revealed that the cost per patient managed with 99DOTS was strongly dependent on service volume, followed by 99DOTS server support costs ([Fig. 1](https://doi.org/10.1016/j.jval.2021.12.002)). Per-patient service provision costs plateaued if more than 2000 patients (cumulative across all clinics) were managed via 99DOTS ([Fig. 1B](https://doi.org/10.1016/j.jval.2021.12.002)). 99DOTS supply costs, the estimated life-years of equipment, and the discount rate were also notable drivers of the per-patient cost of 99DOTS.

### Cost-Effectiveness

The estimated mean cost per treatment success in the “trial-specific” scenario was \$355 (observed range \$229–\$394). This estimate fell to \$59 per treatment success (95% UR \$50–\$70) if the program could be sustained for at least 5 years (“extended activities”) and further to \$49 (95% UR \$42–\$57) in the “marginal clinic” scenario. Considering incremental (rather than total) treatment successes, 99DOTS was estimated to generate 15.5 additional treatment successes per 100 patients (95% UR 8.33–22.70) at an incremental cost of \$5138 (95% UR \$4429–\$5986) in the “extended

**Table 1.** Total program costs.

Cost category	Weighted mean total cost per clinic, trial specific (observed range)*		Total cost for 18 clinics, trial specific <sup>†</sup>	Total cost for 18 clinics, extended activities <sup>‡</sup> (95% uncertainty range)		Total cost for 18 clinics, marginal clinic <sup>§</sup> (95% uncertainty range)	
Overhead	\$1.77	(0.09-3.13)	\$25	\$142	(93-206)	\$142	(93-206)
Building	\$0.21	(0.01-0.38)	\$3	\$19	(14-24)	\$19	(14-24)
Equipment	\$1306	(1022-1551)	\$23 159	\$6703	(5364-7810)	\$6703	(5364-7810)
Staff	\$47	(2-84)	\$651	\$3711	(2304-5603)	\$3711	(2304-5603)
Supplies	\$208	(4-268)	\$4618	\$18 285	(13 851-23 279)	\$18 285	(13 851-23 279)
Technology support/hosting	\$828	(129-1852)	\$18 051	\$38 852	(34 474-43 492)	\$38 852	(34 474-43 492)
Implementation	\$2877	(2352-3187)	\$53 047	\$18 780	(16 914-20 667)	\$3346	(2219-4455)
Total	\$5268	(3771-6238)	\$99 554	\$86 492	(76 194-93 061)	\$71 058	(60 817-81 924)

\*The mean total cost per clinic. Derived from the total cost at each of the 5 costed sites in the “trial-specific” scenario. Costs are weighted based on the patient service volume seen at each clinic during the trial. The observed range shows the minimum and maximum empirically observed total cost from across the 5 costed sites. The total cost per clinic of each costed clinic is available in Appendix 4 and Appendix Table S4.1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.12.002>.

<sup>†</sup>Trial-specific costs refers to expenses incurred during the study period alone, with no continuation of 99DOTS beyond the trial study period.

<sup>‡</sup>Extended activities assumes a 5-year time horizon for implementation and operation costs.

<sup>§</sup>Marginal clinic assumes 99DOTS system infrastructure was in place, and only additional clinics needed to be added, under a 5-year horizon. It omits preimplementation costs incurred to establish the 99DOTS platform in Uganda.

activities” scenario. This resulted in an estimated incremental cost-effectiveness ratio of \$355 (95% UR \$219-\$623) per additional treatment success (Table 3 and Fig. 2A). The probability of cost-effectiveness (Fig. 2B) was low at 0.11 for a willingness-to-pay threshold of \$250 per treatment success, but sharply rose to 0.92 at a \$500 threshold.

## Discussion

We performed an economic evaluation of 99DOTS, a low-cost DAT designed to support TB treatment, in the context of a

multicenter implementation trial in Uganda. Our findings show that 99DOTS can be effectively implemented as an option to facilitate TB treatment completion at a reasonable cost. In particular, assuming that trial activities could be programmatically extended for 5 years, 99DOTS was estimated to cost \$59 per treatment success overall and \$355 per additional (incremental) treatment success. To put these costs in context, TB contact investigation in Uganda has been estimated to cost \$877 per incremental TB diagnosis.<sup>22</sup> A recent study estimated that 1 episode of drug-susceptible TB treatment in Uganda would cost \$396 (in 2017 USD), similar to a more general estimate of \$422 for patients and \$317 for providers (2019 USD) to treat drug-susceptible TB in

**Table 2.** Cost per patient and per treatment success by scenario.

Cost category	Trial specific*		Extended activities <sup>†</sup> (95% uncertainty range)		Marginal clinic <sup>‡</sup> (95% uncertainty range)	
	Mean cost per patient (observed min + max)	Mean cost per treatment success (observed min + max) <sup>§</sup>	Mean cost per patient (95% uncertainty range)	Mean cost per treatment success (95% uncertainty range)	Mean cost per patient (95% uncertainty range)	Mean cost per treatment success (95% uncertainty range)
Overhead	\$0.08 (0.04-0.13)	\$0.10 (0.04-0.16)	\$0.08 (0.06-0.11)	\$0.10 (0.07-0.13)	\$0.08 (0.06-0.11)	\$0.10 (0.07-0.13)
Building	\$0.01 (0.01-0.12)	\$0.01 (0.01-0.02)	\$0.01 (0.01-0.01)	\$0.01 (0.01-0.02)	\$0.01 (0.01-0.01)	\$0.01 (0.01-0.02)
Equipment	\$78.33 (51.47-643.42)	\$91.96 (64.33-99.87)	\$4.01 (2.93-5.30)	\$4.63 (3.35-6.16)	\$4.01 (2.93-5.30)	\$4.63 (3.35-6.16)
Staff	\$2.23 (1.12-3.44)	\$2.62 (1.11-4.30)	\$2.19 (1.44-3.12)	\$2.53 (1.66-3.62)	\$2.19 (1.44-3.12)	\$2.53 (1.66-3.62)
Supplies	\$9.87 (1.93-10.70)	\$11.59 (1.93-12.01)	\$10.78 (9.41-12.03)	\$12.46 (10.69-14.19)	\$10.78 (9.41-12.03)	\$12.46 (10.69-14.19)
Technology support/hosting	\$37.69 (16.69-64.31)	\$44.25 (17.97-92.60)	\$23.10 (19.71-27.19)	\$26.69 (22.51-31.76)	\$23.10 (19.71-27.19)	\$26.69 (22.51-31.76)
Implementation	\$174.47 (112.67-1408.42)	\$204.81 (132.79-246.58)	\$11.22 (8.76-14.30)	\$12.97 (10.01-16.69)	\$2.00 (1.25-2.90)	\$2.31 (1.43-3.38)
Total	\$302.69 (219.87-2119.14)	\$355.33 (229.03-394.04)	\$51.39 (44.30-59.86)	\$59.39 (50.31-70.09)	\$42.17 (36.57-48.86)	\$48.73 (41.86-56.70)

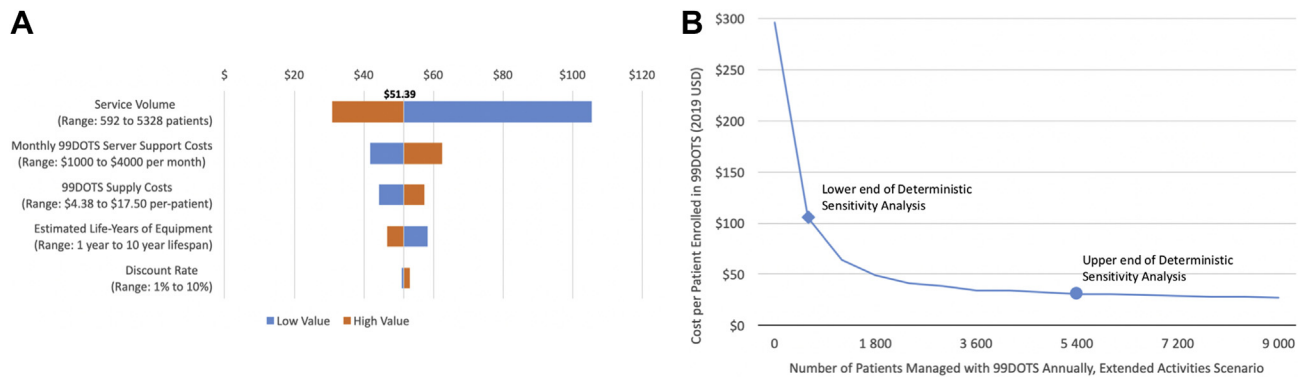
\*Trial-specific costs refers to expenses incurred during the study period alone, with no continuation of 99DOTS beyond the trial study period.

<sup>†</sup>Extended activities assumes a 5-year time horizon for implementation and operation costs.

<sup>‡</sup>Marginal clinic assumes 99DOTS system infrastructure was in place, and only additional clinics needed to be added, under a 5-year horizon. It omits preimplementation costs incurred to establish the 99DOTS platform in Uganda.

<sup>§</sup>Excludes clinic 1 because there were no observed treatment successes during the trial period.

**Figure 1.** Results of deterministic sensitivity analysis. (A) The estimated cost per patient in the “extended activities” scenario under 1-way variation of parameter. Blue bars represent the minimum value of the parameter; orange bars represent the maximum value of the parameter. Only the 5 most influential parameters are shown. 99DOTS supply costs refers to airtime and expenses to print, package, and ship the 99DOTS treatment envelopes. (B) The relationship between the cost per patient and the number of patients managed annually across the 18 study clinics in the “extended activities” scenario. The diamond point represents the minimum value of the deterministic sensitivity analysis from panel A, and the circle represents the maximum value of the deterministic sensitivity analysis from panel A. All values presented in 2019 USD. USD indicates US dollars.



high-burden countries.<sup>23,24</sup> 99DOTS would be expected to add less than 20% to the health system cost of treating drug-susceptible TB, at a cost per incremental treatment success that is qualitatively similar to the cost per incremental diagnosis of another recommended TB intervention.<sup>25</sup> Thus, even without the need to estimate additional benefits of reduced transmission and emerging drug resistance, 99DOTS is likely to be cost-effective relative to other recommended interventions for TB.<sup>22–24</sup>

Both the cost and cost-effectiveness of 99DOTS were strongly influenced by annual service volume, the length of time 99DOTS is operational, and the degree to which initial investments in infrastructure can be scaled up to reach larger numbers of patients over time. For example, tripling the number of patients managed with 99DOTS was estimated to lower the cost per patient from \$51 to \$31 (with the cost plateauing at approximately \$27 at high service volumes). These volumes may be readily achievable programmatically, given that 20.3% of potential participants were excluded by the study’s enrollment criteria.<sup>15</sup>

The largest determinants of per-patient costs were supplies (21.0%), implementation (21.8%), and 99DOTS server support (45.0%). To make 99DOTS more affordable, policy makers should target reducing these expenses. Of note, although the costs of implementing 99DOTS can be substantially reduced on a per-patient basis simply by scaling up the program (as shown by our “extended activities” and “marginal clinic” scenarios), the costs of supplies and—to an extent—server support made it difficult to reduce costs below \$25 per patient managed, even at high service

volumes. 99DOTS envelopes were printed in India and shipped to Uganda, leading to high supply costs. In an ongoing programmatic scale-up study, 99DOTS envelopes are now locally produced; therefore, lower supply costs are anticipated. Furthermore, 99DOTS is an open-source platform; as such, server support costs may also be reduced by establishing an in-country server or running the 99DOTS system platform through a third party.

To the best of our knowledge, this is one of the first studies to empirically measure the costs, inclusive of implementation costs, of DATs for TB treatment in a high-burden setting. Our analysis uses data from a pragmatic clinical trial and considers both “real-world” and “trial-specific” situations. Our estimates of 99DOTS costs are comparable with those from other published studies in high-burden settings. A decision analysis model estimated a cost of \$394 (2016 USD) per person managed with 99DOTS in Brazil, based on published cost estimates (ie, without empiric costing).<sup>13</sup> A study from South Africa in 2012 estimated a cost of \$706 per patient for the SIMpill system, an SMS-based technology that logs when a pill bottle lid is removed.<sup>10</sup> A more recent study from Morocco using a smart pillbox to track TB adherence found a cost of \$321 per patient, but did not provide further cost-effectiveness outcomes.<sup>11</sup>

Our results should be interpreted in light of certain limitations. First, our estimates of cost-effectiveness are based on the per-protocol effectiveness estimates from the primary trial. When analyzed under the intention-to-treat principle, no difference was found when comparing the 99DOTS and routine care arms.<sup>15</sup> The

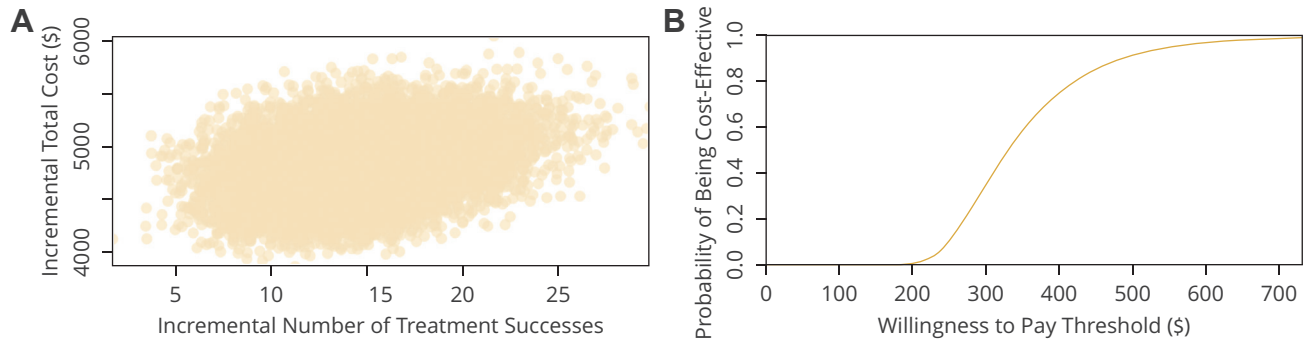
**Table 3.** Incremental cost-effectiveness of 99DOTS, extended activities scenario.

Study arms	Total cost per 100 patients, extended activities (95% uncertainty range)	Number of treatment successes per 100 patients (95% uncertainty range)	ICER (95% uncertainty range)*
Intervention	\$5138 (4429-5986)	86.63 (81.12-92.12)	—
Routine care	—	71.13 (66.62-75.64)	—
Increment	\$5138 (4429-5986)	15.49 (8.33-22.70)	\$354.60 (219.16-623.06)

ICER indicates incremental cost-effectiveness ratio.

\*The ICER does not exactly equal the incremental cost divided by the incremental effectiveness, because it is calculated separately in each simulation (10 000 iterations).

**Figure 2.** Incremental cost-effectiveness results from the Monte Carlo simulation. (A) The incremental cost-effectiveness plane for cost per treatment success. Each dot represents a single simulated clinic. The x-axis is the incremental effectiveness, how many additional treatment successes there are per 100 patients with the 99DOTS intervention, compared with routine care. The y-axis is the incremental cost, showing the total additional cost of the 99DOTS intervention per 100 patients, compared with routine care. (B) The cost-effectiveness acceptability curve. The x-axis shows different willingness-to-pay thresholds, how much a stakeholder is willing to pay per additional treatment success with 99DOTS compared with routine care. The y-axis shows the probability of 99DOTS being cost-effective at a given willingness-to-pay threshold. All values presented in 2019 USD. USD indicates US dollars.



per-protocol effectiveness results are likely subject to selection bias, in that those who enrolled on 99DOTS may have been more likely to complete treatment. Nevertheless, among participants enrolled on 99DOTS, treatment completion was very high (and better than for participants who did not enroll on 99DOTS), suggesting that—for the more than half of patients who would enroll on 99DOTS if offered—99DOTS represents an important and patient-centered alternative for treatment monitoring.<sup>15</sup> Therefore, our analysis (using the per-protocol results) should be interpreted as providing data on the conditions influencing the cost and cost-effectiveness of 99DOTS for patients who would choose this as an option for treatment support if offered, not as a universal policy for all patients with TB in Uganda. Second, with an exception to certain site-level costs routinely logged for study operations purposes, we relied on empiric data from select study sites that served as proxies for remaining sites in calculating total costs of 99DOTS delivery. Nevertheless, the 5 selected costing sites closely represent a range of different operational characteristics and we used the average cost, with URs, to assess a range of total intervention costs in our analytic scenarios. Third, building, overhead, and training costs (part of implementation) were unavailable from one of our 5 clinics. We used the average cost from the other clinics as a proxy for these data, which were not a major determinant of overall costs. Fourth, the average service volume in the 5 clinics where costing was performed was 35% lower than in the other 13 study clinics. This is attributable primarily to the costed clinics being randomized to a shorter duration of time in the intervention arm. As a result, our “trial-specific” cost estimates may be substantially overestimated—but estimates in the “extended activities” and “marginal clinic” scenarios are unaffected, because service volume in those scenarios is standardized to annual rates. Finally, our cost and cost-effectiveness analyses only considered incremental programmatic costs to TB treatment if 99DOTS was used to manage patients and our cost-effectiveness estimate was based on incremental treatment success. In terms of costs, we expect that increased retention in care will likely increase incurred costs of TB drugs and routine clinic visit costs (used by those 10%–15% of patients who would otherwise not stay adherent if 99DOTS were not available). Nevertheless, we also expect that these would be marginal compared with the programmatic costs, and increased treatment adherence will likely save health systems money when factoring costs of complications

that results from nonadherence (eg, longer treatment duration, relapse, development of drug resistances).<sup>13</sup>

## Conclusions

99DOTS has been promoted as a low-cost, scalable intervention to help patients with TB adhere to treatment.<sup>15</sup> Until now, this assertion has lacked a strong empiric evidence base. Our study aimed to bridge this gap by costing the implementation of 99DOTS in Uganda. Our findings suggest that 99DOTS can be implemented in high TB-burden regions at reasonable per-patient cost, with an incremental cost per treatment success that is lower than the societal cost of treating TB more generally. The costs and cost-effectiveness of 99DOTS were strongly influenced by service volume and the degree to which initial investments in infrastructure can be scaled up to reach larger numbers of patients over time. Reductions in 99DOTS supply and server costs could make this intervention even more cost-effective. Future efforts should explore the sustainability of the 99DOTS platform, the costs and effectiveness of 99DOTS in other resource-limited settings, and the feasibility of scaling up this promising technology under existing budget constraints.

## Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2021.12.002>.

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**Accepted for Publication:** December 2, 2021

**Published Online:** January 6, 2022

doi: <https://doi.org/10.1016/j.jval.2021.12.002>

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**Conflict of Interest Disclosures:** The authors reported no conflicts of interest.

**Funding/Support:** This project was supported by the Stop TB Partnership's TB REACH initiative (grant number STBP/TBreach/GSA/W6-37: Dr Adithya Cattamanchi, Dr Achilles Katamba), which is funded by the Government of Canada, the Bill & Melinda Gates Foundation, and the United States Agency for International Development.

**Role of the Funder/Sponsor:** The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Acknowledgment:** The authors thank the staff, patients, and administration at participating health facilities for their support and the DOT to DAT research team for their involvement and oversight of the study. The authors are grateful for all the assistance and collaborative efforts provided by the Uganda National Tuberculosis and Leprosy Program, the district TB focal persons, and health facility staff in implementing the DOT to DAT trial. The authors also extend our gratitude to Pankti Shah and Amy Chen at Everwell Health Solutions for assisting with cost data for 99DOTS packaging and server maintenance.

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