# 99DOTS: A Low-Cost Approach to Monitoring and Improving Medication Adherence

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## ABSTRACT

Ensuring that patients adhere to prescribed medication remains an important challenge in global health. While technology has been utilized to monitor and improve adherence, solutions to date have been too costly for large-scale deployment in developing regions. This paper describes 99DOTS, a low-cost approach for tracking adherence using a combination of paper packaging and low-end mobile phones. Every day, patients reveal an unpredictable phone number behind the pills and send a free call to that number to indicate that drugs were dispensed and taken. Within five years of its inception, 99DOTS has become a standard of care for tuberculosis in India and has enrolled over 200,000 patients. We provide a holistic account of the project's evolution, including its iterative design, scaled implementation, and lessons learned along the way. We hope this account will serve as a useful case study for anyone seeking to establish and scale new low-cost technologies for a global audience.

## CCS CONCEPTS

• **Human-centered computing → Empirical studies in HCI**;

## KEYWORDS

99DOTS, medication adherence, tuberculosis, India, HCI4D, ICTD

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## 1 INTRODUCTION

The World Health Organization estimates that only half of chronic disease patients take medication as directed [14]. This challenge is increasingly important in global health, as chronic disease is projected to account for almost three quarters of global deaths by 2020 [63]. While medication adherence may seem like a simple problem, it has emerged as a deep psychological, sociological, and logistical challenge [16, 17, 58]. Though some successful adherence interventions do exist, many seem to fail, and overall rates of adherence have remained nearly unchanged in recent decades [16].

Medication adherence is especially important for tuberculosis (TB): a bacterial infection, spread by coughing, that is now the largest infectious killer in the world. TB claims over 1.5 million lives per year, even though it is generally curable with drugs that are free in most countries. However, the treatment course is demanding, requiring patients to consume daily (or alternate-day) medications for at least six months. Failure to adhere to treatment or sustain treatment for the recommended duration has been strongly associated with recurrent TB, furthering TB transmission in communities. Non-adherence can also contribute to drug-resistant TB (DR-TB), which is much more difficult to treat. As of 2018, medication for treating DR-TB costs over $1000 per patient (versus $40 for drug-sensitive TB), and the global treatment success rate is only 55% (versus 82% for drug-sensitive TB) [64]. With roughly a half-million new cases emerging each year, drug-resistant TB has become an urgent priority for rich and poor countries alike.

The longstanding globally-recommended strategy for managing tuberculosis is called Directly Observed Therapy (or DOT). An unusual aspect of DOT is that it takes custody of the drugs away from the patient. In order to take medication, a patient usually needs to report to a health center, where drugs are dispensed and a health worker directly observes the ingestion of pills. While DOT has been successful in increasing engagement between patients and health workers, there are concerns about its effectiveness as well as the burdens placed on patients [30]. In India, for example, patients receiving DOT need to travel to a health center over 40 times for dosage observation. This travel often led to missed work or home responsibilities, increased financial expenditures, experiences of stigma at health centers, and other challenges [34, 43, 44].

Recently, there have been hopes that digital technologies could help to restore patients' dignity and autonomy, enabling them to retain custody of their medications while still achieving the therapeutic and public health goals sought via DOT [40, 57]. For example, devices such as electronic pillboxes have been shown to monitor dosage accurately [32, 59] and can automatically remind patients and alert caregivers of any missed doses. Usage of such devices has been shown to improve adherence, both in rich countries [18] as well as for TB patients in China [39]. However, conventional electronic pillboxes (with cellular interface) cost at least $100 each.

In this paper, we describe a new approach for monitoring medication adherence that is specifically designed for the capabilities and constraints of low-resource areas. Called 99DOTS,[1] our system uses a combination of paper packaging and low-end mobile phones to validate that pills have been dispensed. As illustrated in Figure 1, a custom paper envelope is wrapped around each blister back of medication and sealed shut by a care provider. When patients dispense pills, they break through perforated flaps on the back of the envelope, revealing a hidden, unpredictable phone number. Patients use an ordinary phone (usually their own or a relative's) to place a free call to this number, which a computer answers, says "thank you", and hangs up. From this simple interaction—the combination of the patient's registered caller ID and the sequence of unpredictable numbers that they call over time—we can check that pills were dispensed and likely taken. In addition to this mechanism for reporting adherence, 99DOTS also supplies supporting ICT tools for health workers, enabling them to efficiently monitor and respond to any missed doses. Our ultimate goal is not only to measure adherence, but to improve it via targeted counseling and intervention.

Starting from early pilots five years ago, 99DOTS has grown to become part of the standard of care for TB patients in India. As of October 2018, it has enrolled over 200,000 patients, including nearly every public-sector TB patient across five states and every public-sector TB-HIV coinfected patient across India. It has also expanded internationally, with 1,650 patients enrolled in Myanmar. This paper tells the story of the 99DOTS project to date, spanning its design, implementation, scale-up, and lessons learned along the way. While a rigorous impact evaluation is only in the initial stages, we present current usage trends and outline our approach to future evaluations. In addition to its relevance to those working on medication adherence, we hope this paper can serve as a useful case study for anyone seeking to establish and scale a low-cost technology intervention in developing regions.

## 2 RELATED WORK

The benefits and drawbacks of using DOT in TB treatment have been well studied. Compared to self-administered drugs, some studies found that DOT offered benefits [33] while others found no difference [66]. Patients undergoing DOT have faced hurdles with the time and cost of travel, inconvenient hours of centers, long waiting times, lack of privacy, public stigma, compromised home commitments and lost earning opportunities [34, 43, 44].

In part due to these challenges, the World Health Organization (WHO) has concluded that adherence interventions are required to ensure good treatment outcomes [65]. While recent reviews have called for more evidence regarding the impact of digital technologies on tuberculosis treatment [45], the WHO has endorsed a set of digital adherence technologies, including 99DOTS [46].

[1] 99DOTS aspires to preserve 99% of the benefits at 1% of the cost


(c)

**Figure 1: Overview of 99DOTS. (a) Drugs are wrapped in a paper envelope and (b) sealed shut by a provider. (c) Patients dispense pills, reveal an unpredictable phone number, and place a free call to that number to indicate drugs are taken.**

Digital pillboxes are another approach used to monitor medication adherence [1, 10, 11]. The Aardex MEMS device, which counts the number of times that a pillbox is opened, has been used in over 700 clinical studies [13, 58, 59]. However, traditional electronic pillboxes have not been appropriate for global TB programs: they are designed around loose pills as opposed to blisters (which are often used for TB) and are very expensive.

To overcome these hurdles, a recent pillbox has been designed to hold entire TB blister packs while being as affordable as possible. Called evriMED, this device has been piloted with nearly 10,000 TB patients in China and 2,000 patients in both India and Africa. A randomized trial showed improvements in adherence, as measured by box openings and pill counts, and a trial is underway to assess health outcomes and cost-effectiveness [38, 39]. Compared to 99DOTS, an electronic box offers the benefit of automatic dosage logging, without requiring daily effort (or phone access) by patients. However, 99DOTS offers greater affordability, as well as portability for patients who take medication outside their home.

Another way of using mobile phones to reduce the burden of DOT is for patients to record videos of themselves swallowing medication for remote verification. Known as Video Directly Observed Therapy (VDOT or VOT), this approach has been validated [20, 28, 29, 55, 56, 61] and is being commercialized [2, 4, 9]. While VDOT offers high confidence that drugs are taken, it is not an immediate match for most patients in India due to its dependence on smart phones and Internet access. Also, some demographics in India (women, religious minorities, etc.) may not be very comfortable appearing on video, especially given the stigma of TB.

Researchers have also worked to improve the transparency and accountability of DOT programs. In a project called eCompliance, biometric fingerprinting technology is used to verify that health workers and patients meet as intended [17, 48]. Experience from eCompliance helped motivate the design of 99DOTS, since strict enforcement of DOT revealed common situations in which patients need to take drugs remotely. The two approaches are complementary and could be used together, as eCompliance tracks in-person dosing and 99DOTS tracks remote dosing.

Mobile phone reminders using SMS or automated calls have received broad interest as a tool to promote medication adherence. While some interventions have led to positive impact on adherence [37, 47], others have shown no effect [42, 54]. Such mixed results reiterate that no particular technology is guaranteed to offer benefits. New innovations need to be closely matched with the specific needs and latent opportunities in a given treatment context.

Advanced sensors have also been developed for TB medication adherence. An ingestible digital pill has been piloted with tuberculosis patients [16]. Others sought to develop a urinalysis strip that reveals a hidden code (redeemable for mobile airtime) after use by adherent patients [15]. Both initiatives, while provocative, have yet to demonstrate affordability or societal acceptance.

Printing codes on blister packs has also been used to counter medication counterfeiting [7, 8], and can indirectly measure adherence if patients validate every blister pack received. However, each anti-counterfeiting code is unique, and hence is longer or more complex than phone numbers. Also, these systems track medication at the granularity of blister packs rather than individual pills.

There are numerous platforms that provide patient management tools similar to 99DOTS. Examples from our research community include CommCare [3], ODK Clinic [14], Medic Mobile [5], HIS [53] and OpenMRS [6]. The use of mobile reminders to improve health worker accountability and performance has been demonstrated [26]. Patterns underlying the success [35] and failure [25] of mHealth projects have been described.

Researchers have also studied the interplay of paper and technology in developing regions [23, 31], developed hybrid tools that leverage paper in new ways [41, 49, 52, 62] as well as making it easier to interpret paper records in digital form [19, 21, 22].

## 3 TECHNICAL INNOVATION

*Key Ideas.* The innovation underlying 99DOTS can be distilled to two key ideas. The first idea is to modify medication packaging to embed hidden codes behind the pills, and for patients to report those codes as evidence of having dispensed medication. While we considered this idea as early as 2009, we originally assumed that each code would need to be unique: a long numeric or alphanumeric string, difficult to guess, that appears in only one pill compartment and thereby proves that a new pill was dispensed. While there are various ways of submitting such codes to a server, none is obviously inclusive of low-income users. For example, SMS is expensive[2] and not widely used[3] among low-income populations in India; Interactive Voice Response (IVR) often requires training for first-time users [36, 50]; USSD is not easily customizable in India (though may be elsewhere [51]); and applications relying on smart phones and/or Internet connectivity are not universally accessible. These hurdles prevented us from pursuing the idea at the time.

The second insight underlying 99DOTS is that, because chronic disease patients take medication over long periods of time, we can observe and verify *sequences* of codes as opposed to verifying each individual code in isolation. Even if the set of valid codes is known to patients, so long as the sequence of codes is unpredictable, we can analyze that sequence and check whether it corresponds to a valid pattern hidden within a blister pack.

In other words, 99DOTS represents a tradeoff between the cost and accuracy of the encoding scheme. By decreasing the number of hidden codes—say, to less than 100 different codes—it becomes possible for each code to represent a phone number that is owned by us. Instead of submitting a code *to* a given phone number, patients submit the code by briefly calling the number itself. The only sacrifice made for this newfound simplicity is that the system can no longer provide an absolute guarantee that any individual code submitted (number dialed) corresponds to a new pill dispensed. Instead, the system offers a probabilistic and time-varying guarantee that the sequence of dialed numbers corresponds to a sequence of pills dispensed. While this weakened guarantee may be insufficient for critical applications such as banking, it is often sufficient in the context of medication adherence, where any amount of confidence gained (relative to unsupervised dosing) is helpful for care providers. Also, incentives for adversarial behaviors (fake reports) are generally lower in the context of medication adherence than in domains such as banking: patients do not stand to gain financially by misrepresenting reports to 99DOTS.

*Checking Call Sequences.* Given a sequence of calls to 99DOTS, we would like to check whether each number dialed was drawn from a freshly opened pill compartment. If a patient calls 99DOTS in a repetitive or random order—for example, from the phone's call history, or from pill compartments that were previously opened—then this behavior should be flagged for review. When we talk about a "guarantee," we are referring to the probability that such repetitive or random calls can be detected by our system.

It turns out that formally characterizing the guarantees offered by 99DOTS is a rich mathematical exercise that we defer for publication in a different venue. For now, we seek only to provide an intuition for how patients' calls can be verified, and to highlight some of the factors that influence that verification. One assumption we make is that patients consume all pills in one blister pack before moving on to the next one; otherwise, many more call sequences are valid and the guarantees become much weaker. In practice, this implies that if a patient interleaves calls from multiple blister packs, that behavior may be flagged as if it were repetitive or random calling.

There are simple and efficient algorithms that can calculate a lower bound on the number of mistakes or misrepresentations that a patient makes while calling 99DOTS. The inputs to the algorithm are (i) the sequence of 99DOTS numbers called over time, and (ii) the set of number sequences that are hidden on the blister packs. The algorithm uses dynamic programming to calculate an alignment score between every subsequence of the call sequence and every hidden number sequence on the blister packs. Then, it infers which assignment of blister packs to days leads to the highest overall alignment score for the entire sequence. The number of calls that are successfully aligned with some blister pack are deemed

[2] In India it is challenging to set up a toll-free SMS number, which implies that users would need to pay for the messages sent.

[3] In 2016, we conducted a phone survey with 105 TB-HIV patients. Only 19% claimed that they were able to send and receive SMS. The vast majority (72%) said that they do not use SMS; a small fraction (5%) said that they can read SMS but not send it, and the same proportion (5%) said that they can recognize an SMS but do not understand it.

to be valid as per 99DOTS. Other numbers must have been dialed incorrectly by patients, i.e., by either accidentally or deliberately repeating numbers without opening new pill compartments.

There are some basic properties of this algorithm that are useful to understand. While there may be some incorrect calling behaviors that go undetected by the algorithm (false negatives), every mismatch that is flagged by the algorithm is guaranteed to correspond to some real deviation from the call sequence (there are no false positives). One subtlety, however, is that the algorithm cannot always pinpoint the exact day(s) on which a patient made a mistake. For example, the algorithm could show that the patient made at least one calling error during the second week of treatment, but the error may have occurred on one of several days, depending on which blister pack the patient actually used. This uncertainty adds some complexity to how the results of the algorithm are displayed to users. For now, we display only the most common mistake—calling the same number for several days in a row—as a direct visualization for health workers. Other mistakes, which have proved far less common and are rarely actionable in the field, are currently managed via customized reports from 99DOTS staff.

There are several parameters that impact how many errors this algorithm can detect. Some of the most important ones are the number of phone numbers available (60 in our India deployment), the number of doses per blister (between 7 and 14 for most TB patients in India), the number of distinct sequences that are printed on blisters (discussed later), and the design of the hidden number sequence itself (a question in coding theory that we defer for a future publication). While a more detailed evaluation is beyond the scope of this paper, our simulations indicate that in our deployment environment, over 90% of errors can be detected.

*Design Evolution.* As we deployed 99DOTS at scale, additional design innovations were needed to adapt the core ideas to real-world constraints. Three examples of these adaptations are as follows.

**(i) Fixed ordering to flexible ordering:** Our original design required patients to dispense pills in a fixed order, starting from one corner of the blister pack and following a dotted line across the remaining compartments. However, analysis of calling patterns showed that only 46% of patients placed at least 90% of calls in the correct order, and follow-up field observations confirmed that instructions regarding the ordering were rarely understood or followed by patients, even when counseling was provided.

This caused us to redesign our envelopes from scratch, with over 25 graphic design iterations, more than a dozen focus groups and field observations of over 100 patients. The result was a major simplification of the envelopes (and supporting algorithms) that allowed patients to dispense pills in any order. (To facilitate counseling, our envelopes still suggest an order of dispensing, which follows the column-wise ordering that is commonly seen on Indian calendars; however, the ordering is not enforced by our algorithms.) After this change, it is more accurate to think about 99DOTS as checking that a given set of dialed numbers appear on a blister pack, as opposed to a given sequence. If patients have higher literacy in future deployments, we would consider fixed sequences again.

**(ii) Digital offset printing to lithographic printing:** In our original design, there were thousands of different sequences printed on 99DOTS envelopes, implying that a patient was very unlikely to see the same sequence more than once. However, manufacturing such envelopes requires a specialized printing process, called digital offset printing (with variable data). As we scaled up, we learned that digital offset printing does not offer the same economies of scale as traditional lithographic printing, in which a set of plates is used to stamp many sheets. When ordering millions of envelopes, lithographic printing was 47% of the cost of digital offset printing. Lithographic printing was also more commonly available.

To adapt to this cost reality, we re-evaluated our assumption as to whether or not patients needed to receive a different sequence with every blister. The number of distinct sequences is subject to a tradeoff between the ability to detect the reuse of old blisters and the ability to detect a call sequence not connected to any particular blister (e.g., by calling numbers randomly). A higher number of distinct sequences allows for greater confidence in detecting reuse of an old blister, since it is less likely for a patient to receive the same sequence twice. A lower number of distinct sequences allows for greater confidence in detecting incorrect sequences, since the set of valid sequences is smaller. However, even when we had thousands of distinct sequences, we found it difficult to detect blister reuse due to intermittent calling patterns. Thus we were happy to accept the tradeoff in favor of detecting incorrect calling sequences and a lower cost through lithographic printing.

Consequently, we shifted our approach to manufacture only 50 different envelope designs for each medication. Each design is printed in bulk with a separate lithographic plate and interleaved manually prior to distribution. This change implies that we are no longer able to offer any practical guarantee of detecting reuse of a blister by a patient, since many patients will receive at least one blister sequence more than once. However, with 50 different designs we believe that most patients (and health workers) will be unable to notice when the same design is repeated.

**(iii) Weight-wise envelopes to universal envelopes:** One advantage of working in tuberculosis is that there are standard form factors of medication that are used by most governments around the world. Each blister contains 28 pills. However, one inconvenient aspect of this medication is that dosing depends on weight: patients consume between 2 and 5 pills per day. In order to enable each category of patient to reveal exactly one hidden number per day, we originally designed and manufactured four different versions of the envelopes (one for each weight band). However, at scale we found that some centers would run out of stock of a given envelope, inhibiting treatment of those patients. Supplying sufficient surplus stock in each weight category was costly, especially in centers with unpredictable patient counts. Finally, maintaining four different envelope designs was unsustainably complex, as each required separate estimation, maintenance and fulfillment of inventory across a pipeline of manufacturers, distributors, and centers.

In response, we shifted to a single "universal envelope" with a fixed pattern of 14 hidden numbers (one behind every other pill). Lightweight patients reveal one number per day, average weight patients reveal either 1 or 2 numbers per day, and heavier patients reveal 2 numbers per day (up to 3 per day for the heaviest patients). If multiple numbers are revealed, patients can dial any one of them. This change is a bit uncomfortable because it increases the complexity for patients. It also weakens the guarantees offered by 99DOTS, since the number of valid call sequences increases significantly. However, the improved simplicity of managing the supply chain was absolutely necessary to sustain 99DOTS at scale.

## 4 USAGE SCENARIO

Translating the core ideas of 99DOTS into a practical system that benefits patients, health workers, and supervisors is a significant undertaking. This section describes the broader ICT ecosystem supporting 99DOTS, its intended usage scenario, and the expected value proposition for each of the stakeholders above.

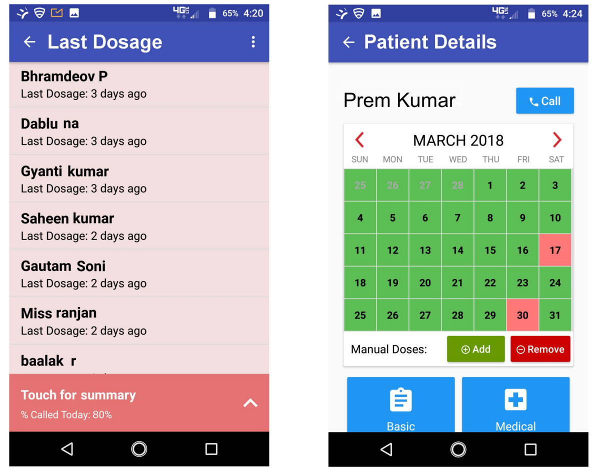
*Patient Experience.* Patients receive medication that has been wrapped in 99DOTS envelopes. One benefit of using secondary packaging is that it provides space for culturally appropriate dosage instructions that are notably absent from the blister packs themselves. The outside of 99DOTS envelopes displays colorful pictograms and local-language text that reinforces key messages about TB treatment as well as intended usage of 99DOTS.

At the time of treatment initiation, patients are counseled on how to use 99DOTS. Usage requires regular access to a phone, which may be the patient's personal phone or a phone that is shared with others. Because access and use of particular phones often varies over time, patients are asked to provide as many contact numbers as possible at the time of enrollment. Incoming calls from any of these numbers indicate a dose taken for the patient. Rarely, two active patients share the same phone, in which case we do not attempt to distinguish which calls are from which patient. Calls from such numbers are linked to both patients and colored differently in the health worker's view.

To use 99DOTS, patients dispense pills through perforated flaps on the back of the envelopes. For every dose, patients open at least one flap with a hidden number printed on the back and use any registered phone to place a free call to the revealed number. A computer automatically answers the call, says "thank you", and hangs up. (While it may sometimes be possible to use a "missed call", in which the phone rings but is not answered, in India our missed call numbers were eventually blocked, as we describe in Section 6.2.)

If a patient does not call 99DOTS on a given day, they receive an escalating series of dosage reminders. First is an automated SMS message, though such messages are not necessarily read by our target demographic. If additional doses are missed, the patient can expect personal outreach from a health worker, either via a phone call or house visit. We are also piloting automated voice messages that periodically offer patients an overview of their recent adherence, including nudges to improve dosing when needed, as well as monthly refill reminders.

While correct usage of 99DOTS may give strong evidence of dispensing pills, it does not prove that pills are swallowed. However, data from other contexts suggests that pills monitored to the point of disbursal are almost always taken [32, 59]. Moreover, patients who are intent on skipping their medications have little incentive to call 99DOTS. Patients' foremost incentive to call is to retain custody of medications they are taking: a basic human dignity that we take for granted in almost every medical situation, but yet is far from standard in the treatment of tuberculosis. Patients who do not report high adherence via 99DOTS may be transitioned to more frequent DOT or other forms of adherence monitoring. Patients are also told that calling 99DOTS keeps their caregivers informed about their treatment, which helps to ensure a full recovery.




(a) (b)

**Figure 2: Screenshots from 99DOTS mobile application: (a) view of patients who recently missed doses and are prioritized for counseling; (b) detailed dosing history for a patient.**

*Health Worker Experience.* In many treatment programs, each patient is assigned to a health worker who is responsible for ongoing counseling of the patient, monitoring medication adherence and ensuring treatment completion. In DOT programs, health workers traditionally observe a subset of doses in person. If patients do not come to treatment centers as scheduled, health workers are responsible for following up with them via phone outreach and house visits. Using 99DOTS, health workers have the added capability of remotely observing doses as reflected by the 99DOTS call logs. The most common interface that health workers use for 99DOTS is a mobile application (see Figure 2); however, they can also access the same information on an Internet website or can elect to receive a subset of the information via SMS. While 99DOTS started as a project to track medication adherence, the ICT platform has evolved into a full-featured patient management system, tracking medical details pertinent to tuberculosis as well as patients' progression through diagnosis, treatment, and an eventual treatment outcome.

One of the potential benefits of 99DOTS is that health workers can offer *differentiated care*: changing when counseling is offered, and what counseling is offered, based on the unique characteristics of each patient. Patients who have missed recent doses on 99DOTS can be prioritized for outreach using a variety of metrics. For example, one metric highlights patients who reported dosage two days ago but missed a dose yesterday, indicating that they were recently able and willing to call, but did not call thereafter. The application can also sort patients by alternate metrics, such as the number of days since their last dose (Figure 2a), their average adherence over the last week, adherence over the last month, and so on. For health workers lacking access to a smart phone, similar missed dose alerts are provided via SMS.

Health workers can also leverage patients' dosing histories to improve the quality of counseling. As illustrated in Figure 2b, the mobile application includes a color-coded adherence calendar for each patient, illustrating days that drugs were reported taken (green) and missed (red). If a patient calls the same number for three or more consecutive days, this is flagged with an exclamation point on the corresponding days. When patients come to refill medication, this calendar can focus the conversation, for example, to review reasons for missing medication on specific days, or to elucidate behavioral patterns that may lead to non-adherence (say, doses missed on weekends, during travel, or during festivals). In addition to prompting personalized counseling for patients, collaborative review of dosing histories may help to engage patients in their treatment.

An additional benefit for health workers is the ability to streamline their workflow. As the system provides reliable dosage monitoring without direct observation, it allows reducing the frequency of patient visits, which reduces overheads for both patients and health workers. The ability for center staff to collaboratively update and quickly access patient information (including details such as the most recent list of contact numbers) can improve efficiency. Finally, the dosing history and other information captured by 99DOTS can reduce the overhead of paper-based reporting that is typically required of health workers.

One feature that proved essential for eventual uptake by health workers was the ability to manually indicate that doses were taken or missed on given days, independent of the 99DOTS call logs. Such "manual doses" are intended for cases where patients are not able to use 99DOTS for any reason. Each manual dose should be annotated with a justification as well as the manner in which dosing information was determined (e.g., direct observation, testimony of patient, etc.). Different organizations, districts and states can and do establish different norms on whether and to what extent manual doses should be used. While calls to 99DOTS are intended as the primary metric of adherence, manual doses provide the flexibility to manage and support all patients on the 99DOTS platform, even if they do not frequently engage with the technology.

*Supervisor Experience.* The 99DOTS platform also aims to bolster management of large treatment programs via various visualizations and reports. Aggregate adherence patterns across different locations, granularities and time periods can be tabulated, enabling program administrators to respond with targeted incentives or supervision. The platform can be configured to automatically send reports via email to district, state, or national-level program managers. In some cases these reports are integrated with the agendas of regular review meetings to sharpen conversations around the current achievements and gaps in program implementations.

## 5 PILOT STUDY

Our first exploration of 99DOTS in the real world was a pilot study in collaboration with St. John's Medical College in Bangalore. Due to space constraints, we present only a synopsis of the study here.

*Methods.* Twenty patients consented to using 99DOTS in place of a government DOTS program during their first two months of treatment. However, while the DOTS program required patients to report to the center three times per week, patients enrolled in the study were given one month's supply (32 doses) of medication at a time. In order to continue for the second month of the study, patients had to report high adherence (at most 5 missed doses) during the first month; otherwise patients would return to DOTS, or optionally to the private sector. The study was restricted to first-time, adult TB patients who had regular access to a mobile phone and could commit to returning for at least one follow-up visit.

As a design exploration, patients in the study were randomly divided into two groups. One group received medications with hidden phone numbers, as per 99DOTS. The other group was asked to call the same phone number every day, with directions printed on the outside of each blister pack. This design allowed us to explore whether hidden numbers were an important part of the intervention. As 99DOTS was then a research prototype, there were some minor differences in the form factor of medication packaging, the timing of reminders, the interface for health workers, and other aspects, compared to what is described in this paper.

After the study concluded, detailed semi-structured interviews were conducted with 16 of the patients. Interviews occurred either in person or over the phone, by a researcher fluent in all languages spoken by patients. The interviewer was from an outside institution and was not involved in planning or executing the intervention, potentially reducing response bias [24].

*Results.* Patients were first enrolled on 99DOTS in July 2013. Patients had an average age of 34 (min=19, max=59), an average individual income of $210[4] per month (min=0, max=$327), an average household income of $760 per month (min=$42, max=$6,720), and an average of 10 years of education. While the average patient was better educated and wealthier than most TB patients in India, there was a wide range of participants, including at least one with no formal education. Of the 20 patients, 6 were women.

Patients calling hidden numbers reported 92% of doses taken, and 98% of numbers dialed were in the correct sequence. Patients calling a fixed number reported 95% of doses taken. Seven patients reported 100% adherence throughout the trial. Patients with limited literacy were able to use the system successfully. Only one patient missed more than 5 doses in the first month, which was justified due to travel outside of mobile coverage. Thus, all 20 patients continued on through the second month of the study.

In the qualitative interviews, SMS reminders were cited as the most liked feature by 13 out of the 16 patients. While only 6 of the 16 patients understood the content of the reminders, all of the patients recognized the sender and timing of the message as a trigger to take their medication and place a phone call. At least one patient admitted sending a call to the fixed number even though they did not have their medication with them, which suggests that calls to hidden numbers may be a more reliable indicator of adherence. Several of the patients perceived being monitored as a positive aspect to treatment, adding a sense of responsibility and connection with the hospital staff who cared that they took their pills. The interactivity of two-way communication (reminders and dialed numbers) was also perceived positively. Some patients requested other ways to interact with the system, including a live physician on call. While the medication was provided free to patients, 12 out of 16 patients expressed a hypothetical willingness to pay (up to $3.30 per month) for the future privilege of using 99DOTS in place of DOTS.

Overall, the pilot study offered promising results regarding the potential feasibility and acceptance of 99DOTS, and stirred initial interest in exploring the use of 99DOTS in programmatic settings.

[4]The exchange rate at the time was 1 USD = 60 INR.

# 6 TRANSITION TO SCALE

In the five years following our first research pilot, 99DOTS has grown to enroll over 200,000 patients. In this section, we narrate the steps that enabled a research prototype to achieve this level of scale in a short period of time, as well as iterative design changes that were required to enable ongoing scaling.

## 6.1 Deployment Trajectory

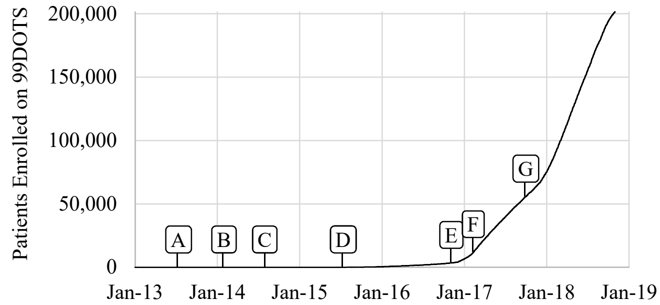
The number of patients enrolled over time is illustrated in Figure 3. The first 20 patients were enrolled in the two-month pilot described previously (milestone A). Though small in scale, this focused and rigorous study provided the evidence needed to approach other partners for larger deployments. We subsequently partnered with two non-profit providers of TB treatment, which started enrolling patients on 99DOTS in 2014 (milestones B and C).

At this point there were two unique circumstances that led to rapid scaling of 99DOTS. The first is that the government TB program was undergoing a major change, which was to replace the longstanding "intermittent regimen" of medications (administered at most three times per week) with a daily dose medication. While there is international consensus that daily medications are better for patients, they posed a predicament for adherence monitoring. Though directly observed therapy was a viable solution for three doses per week, it was feared that patients would find it too burdensome to travel to a treatment center on a daily basis. The ability to track remote administration of drugs was thus viewed not as a "nice-to-have" feature, but as a "must-have" capability, and one that enabled the program to have a strong narrative for adherence monitoring in the new era of daily dose medications.

The second factor that led to rapid uptake of 99DOTS was a unique funding and partnership opportunity, called the Grand Challenges in TB Control. Unlike other opportunities of its kind, winners of this challenge were rewarded not only with funding, but also with direct connections to influential leaders in the government TB program, who had agreed in advance to endorse the winning solutions for pilots in government centers. 99DOTS was fortunate enough to be selected for all three rounds of this competition.

Due to the combination of these factors—an urgent demand for adherence monitoring, and a direct connection between policymakers and ourselves—there was rapid uptake of 99DOTS by the government. For a period of at least two years, the entire supply of new daily-dose medications was bundled with 99DOTS. As these medications were gradually introduced for certain geographies and patient populations, 99DOTS was introduced as well. Deployments started with the population of TB-HIV coinfected patients, which are among the most vulnerable and often prioritized for new interventions: first at 30 high-burden centers (milestone D) and then for every public-sector TB-HIV patient in the country (milestone E). This was followed by a launch for all public-sector TB patients in Mumbai (milestone F) and soon thereafter, every public-sector TB patient across five states (milestone G).

We also pursued several smaller deployments in parallel with those by the Indian government. For example, we have deployed in two public-private partnerships, encompassing 1,860 patients to date. We have also deployed internationally in Myanmar, where 99DOTS has enrolled 1,650 patients to date.




Key Milestones:
A. Pilot with 20 patients in a medical college (Bangalore)
B. Launch with NGO partner in Uttar Pradesh
C. Launch with NGO partner in Bihar
D. Launch for public-sector TB-HIV patients in 30 centers
E. Launch for every public-sector TB-HIV patient in India
F. Launch for every public-sector TB patient in Mumbai
G. Launch for every public-sector TB patient across five states (Maharashtra, Bihar, Kerala, Sikkim, Himachal Pradesh)

**Figure 3: Number of patients enrolled on 99DOTS over time.**

## 6.2 Lessons Learned at Scale

The rapid scaling of 99DOTS caused us to revisit several aspects of the design and implementation. The following paragraphs highlight some of the challenges encountered, and how we adjusted course to overcome those challenges. The data driving our observations originated from numerous channels. In addition to providing on-demand technical support for 99DOTS, we initiated semi-structured conversations in health centers (59 centers visited across 55 districts, interacting with 320 people) as well as in-person training sessions (35 district trainings, 23 state trainings, encompassing 2500 staff).

*Telecom Infrastructure.* As mentioned previously, our original solution required patients to place a missed call to a 99DOTS number. (A "missed call" is one that rings but is not picked up; such calls are often placed intentionally by low-income users in order to send a free signal to another person [27]). However, as our usage volume grew, we discovered that the 99DOTS phone numbers were blocked by certain carriers. Discussions with industry insiders confirmed that telecom companies lose money on missed calls (there is added network congestion without any charge levied) and that numbers receiving large volumes of missed calls may be blocked.

In response, we changed the 99DOTS solution from a "missed call" to a "free call", where users call a toll-free number and hear a short, automated voice message. To make these calls affordable (for us), we negotiated customized billing for a one-second phone call (in India, per-minute pricing is more common, but would have incurred exorbitant costs).

*Patient Experience.* The most important lesson we learned about the patients' perspective is regarding their access to mobile phones. While India boasts over 1.1 billion mobile subscriptions [12] (which is 91% of the population), access to those phones is far from uniform. Though a phone is often accessible to TB patients, that phone is not necessarily a personal phone; often it is shared by a family unit, which implies that it might not be easily accessible to the patient at a given time. In 2016 we conducted a phone survey with 105 TB-HIV patients, all of whom had called 99DOTS at least once. We found that only 64% of patients were using their own phone to call 99DOTS; 30% were using someone else's phone (most commonly a child or spouse) while 6% were using multiple phones. This varying level of access made it difficult for some patients to call 99DOTS, especially if the owner of the phone was working or traveling. To help retain and support patients who did not personally own a phone, we modified the 99DOTS registration form to include as many alternate phone numbers as possible, and to indicate the patient's relationship to each phone listed. We also encouraged patients to report any new phone connections whenever they refill their medications. While phone access remains a challenge for scaled usage of 99DOTS, we have also seen cases where shared phones engender social support for patients, by prompting the phone owner to monitor and report the patient's adherence. Such social support could be studied more in the future.

While toll-free numbers might seem like an easy way to offer free calls to patients, we discovered that additional counseling was needed to ensure successful use of toll-free numbers. The concept of toll-free was not always familiar to patients, and thus required explanation and/or demonstration at the time of enrollment. Patients with prepaid accounts often received an SMS notifying them that Rs. 0.00 had been spent on a toll-free call; some patients (especially low-literate ones) associated such messages with charges to their account. If a prepaid balance is low, patients could hear a long message encouraging them to refill, which sometimes prevented completing the call. We discovered that some patients had negative balance, which prohibited making any calls, even to toll-free numbers. Postpaid users with overdue payments can also be blocked from using toll-free numbers. We eventually distilled these lessons (and others) into a two-page worksheet that proved essential for counselors to easily troubleshoot any issues that patients faced in placing phone calls.

*Health Worker Experience.* We iteratively refined the interface between 99DOTS and health workers in order to make adherence data more accessible, comprehensible, and actionable at scale. Our initial display of adherence information was based on a patient-wise calendar, in which each day is color coded according to the reported adherence that day. While this visualization is useful for facilitating understanding (and is still an important part of our application), we learned that health workers needed to invest additional energy to figure out how to act on the information; for example, which patients to visit or call, and what to discuss with them. In order to decrease this cognitive load, we supplemented the calendar view with a prioritized task list that translates the adherence data into a set of suggested actions, for example, to call a given patient and check why they haven't called 99DOTS in the past few days.

*Supervisor Experience.* A key functionality for supervisors that we did not appreciate originally was the importance of maintaining up-to-date names and contact information for the full hierarchy of staff in a treatment program. While this might sound like a trivial HR function, it turns out to be critically important for any health platform that seeks to alert caregivers about the health status of patients. Moreover, understanding and maintaining a government HR directory proved to be surprisingly complex. Some positions are vacant, implying that certain individuals serve multiple transient roles, or that some responsibilities or alerts should automatically be propagated higher in the management chain. Coordination between multiple agencies, such as the TB division and the HIV division, revealed unexpected complexity, including varying views of recently modified district or state boundaries. Over time, our ICT platform broadened in scope towards a full-featured HR management tool. While sending alerts and notifications is relatively easy, ensuring that the right person gets each message is a harder task.

*Project Management.* It goes without saying that the rapid scaling of 99DOTS transformed the way that our team operated. In 2015, the project outgrew its roots in Microsoft Research and led to the formation of Everwell (now employing 15 people) to champion ongoing scaling efforts. Training sessions for program staff, originally conducted by ourselves, were gradually transferred to a train-the-trainers model. We invested in high-quality print and audiovisual training materials to bolster sessions that we could not attend.

Our model for managing the supply chain also evolved radically. For several hundred patients, we used stickers and tape to manually affix hidden numbers to medication blister packs. For several thousands of patients, we manually glued together printed envelopes and hired our own contractors to wrap drugs in centers. Today, we have multiple vendors who are capable of printing and assembling millions of 99DOTS envelopes at a time. Wrapping of medications is done by program staff, typically at the state or district level. We are working on even closer integration with the medication supply chain, for example, by wrapping medications inside the same pharmaceutical companies that manufacture drugs. While some logistical and regulatory questions remain open, such integration should be technically feasible and very beneficial.

## 7 USAGE AND IMPACT

This section describes how patients engage with 99DOTS in the field and outlines our thinking regarding future impact evaluations.

*Engagement Metrics.* To measure a patient's engagement with a long-term course of medication, two key metrics are *adherence* and *persistence*. We define adherence as the fraction of days that a patient consumes medication (out of all days that they were expected to consume medication). We define persistence as the number of days between treatment initiation and the last day that medication is taken. When using an adherence monitor such as 99DOTS, the *reported adherence* and *reported persistence* may differ from the true values, as they reflect not only the engagement with medication but also engagement with the technology.

To illustrate engagement with 99DOTS, we focus on a long-running deployment, which is Mumbai's public-sector TB program. This program launched 99DOTS across 250 health centers in February 2017. Restricting attention to patients enrolled for at least 30 days as of September 2018, our dataset consists of 27,141 patients. Figure 4 illustrates the reported adherence as measured in two ways: (a) using calls to 99DOTS only, and (b) using calls to 99DOTS in addition to manual annotations by health workers. As mentioned earlier, manual annotations are important for patients unable or unwilling to call 99DOTS, but may overestimate actual adherence.

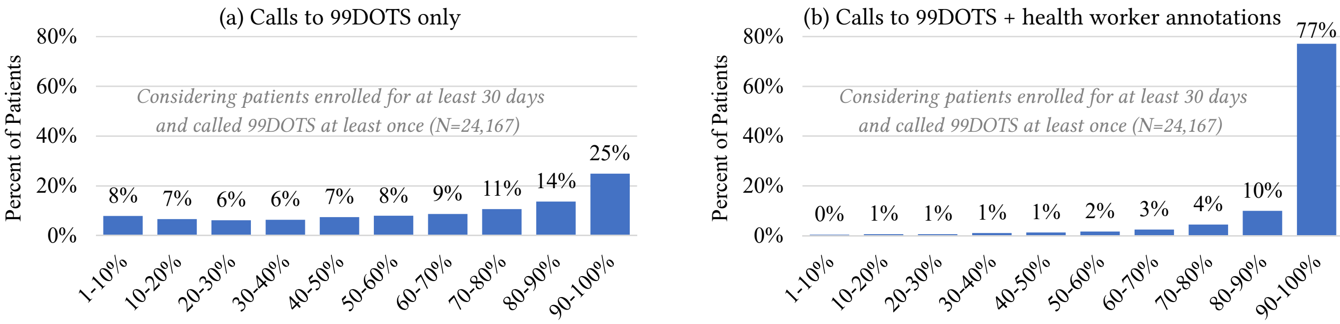



**Figure 4: Reported adherence for Mumbai patients, as per (a) calls to 99DOTS only, (b) calls plus health worker annotations.**

The reported adherence according to calls alone (Figure 4a) is modest. Eleven percent of patients do not call 99DOTS at all; this includes patients who are known to be unsuitable for 99DOTS at the start of treatment (e.g., for lack of phone access). Of patients who called 99DOTS at least once, 39% called for at least 80% of doses. According to health worker annotations (Figure 4b), the actual adherence is higher, with 87% of such patients having a reported adherence of at least 80%. This juxtaposition implies that there are likely many patients who are taking medication without calling 99DOTS. As described previously, this could often be explained by difficulties that patients face in accessing a phone. For this reason, we have come to believe that 99DOTS alone is not sufficient to cover 100% of patients in India; alternate monitoring mechanisms are also needed. Nonetheless, managing a fraction of patients with 99DOTS can offer significant benefits: those patients can be allowed to proceed independently, gaining more autonomy and also relieving the program from daily monitoring obligations.

To understand persistence, we restrict our attention to patients who are currently "on treatment", which means that anti-TB medication is prescribed and expected to be taken.[5] As illustrated in Figure 5, patients on treatment disengage from 99DOTS at a roughly constant rate, with about 90% placing calls for half of the six-month course and 80% placing calls until the final two weeks. A smaller fraction (65%) of patients appear to persist with calls through the full course; however, the steep drop-off in the final weeks could also be explained by inaccuracies in the recorded enrollment date. The reported adherence also drops gradually for patients on treatment, from roughly 75% in the first few days to around 50% in the final days. It is important to note, however, that the adherence represented in Figure 5 includes patients who have stopped persisting. Of patients who persisted for at least 140 days, the average adherence stayed above 70% throughout that period. One limitation of our data is that we cannot distinguish to what extent these trends are explained by changes in actual dosing behavior, versus changes in engagement with 99DOTS. At the very least, it points to the importance of ongoing training and counseling to ensure that patients are engaged with 99DOTS to the maximum extent possible.

*Understanding Impact.* Finding rigorous evidence to quantify the benefits of 99DOTS is one of our highest priorities, especially given the current and projected scale that it has achieved. Such benefits

[5]Patients are on treatment until they are assigned a treatment outcome, such as cured, treatment completed, treatment failed, died, transferred out, or lost to follow-up.

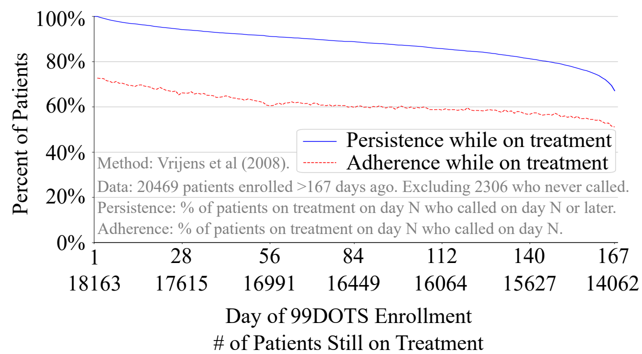



**Figure 5: Adherence and persistence as per calls to 99DOTS.**

could be reflected in a diversity of indicators, including patient health outcomes, accessibility of treatment, cost of administering programs, transparency to administrators and funders, and other metrics. Up until now, we have not had the opportunity to do a rigorous scientific study along any of these dimensions. One barrier to conducting a randomized controlled trial (RCT) in the public sector is that 99DOTS is already considered a standard of care that should be accessible to all patients. As an alternative to an RCT, we are currently undertaking several quasi-experimental studies, including analysis of programmatic data before and after the introduction of 99DOTS. There are also some collaborating institutions that are undertaking an RCT outside of the public sector. All of these studies will take 1-2 years to come to fruition.

Before such rigorous evidence is in hand, there are other reasons for our partners' continued enthusiasm about using 99DOTS. First, as stated earlier, direct observation is burdensome for patients on a daily regimen. 99DOTS offers the potential to relieve that burden for many patients. In fact, even the possibility that *there could exist a solution besides directly observed therapy* (either now or in the future) has arguably been an important factor in enabling India to fully embrace daily-dose medications, which offers other direct benefits for patients.

Second, there are numerous anecdotes suggesting that 99DOTS is improving the accountability of health workers, which in turn can improve the quality of counseling. For example, Figure 6 illustrates the aggregate reported adherence from one of the first TB-HIV centers that adopted 99DOTS. While the initial reported adherence was reasonably high (about 75%), over a period of six months it gradually decreased to 40%—either due to decreased dosing or decreased

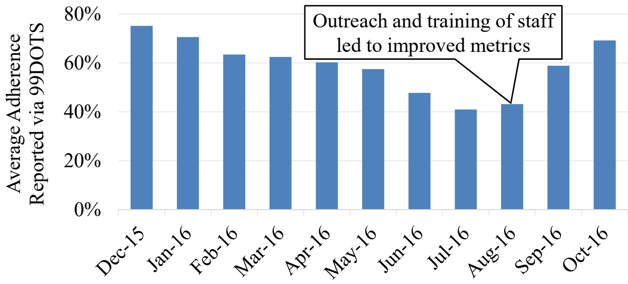



**Figure 6: Aggregate monthly adherence as reported via calls to 99DOTS (from a TB-HIV program in rural India).**

engagement with 99DOTS. This trend was identified and triggered a re-training session, which led to an immediate increase in the metrics. Before 99DOTS, such adherence data was kept on paper and was not aggregated beyond individual patients. With 99DOTS in place, administrators have a real-time transparent view of adherence across every center, district, state, etc., enabling detection, understanding and response to previously unnoticed trends.

Third, there are numerous anecdotal cases where the escalating reminders and alerts provided by 99DOTS have prevented patients from discontinuing treatment. As just one example, one of the first patients in our public-sector deployment called daily for the first two weeks but then suddenly discontinued calling. Upon noticing this behavior, a health worker followed up on the phone and discovered that the patient was experiencing moderate side effects. After basic counseling and education, the patient returned to daily dosing and made a full recovery. Similar data-driven interventions have corrected challenges in understanding the treatment course, the instructions provided in centers, or other aspects of care.

Finally, while 99DOTS started with a sole focus on medication adherence, the ICT platform that was collaboratively developed with the government along the way has since become their official system for managing TB patients in India, independent of the use (or non-use) of 99DOTS as an adherence monitor. Upgrading this platform to modern standards is likely more impactful than 99DOTS itself. It also represents an interesting case study in organizational change. Though the prior TB management platform had several known shortcomings, it proved challenging to update, in part because of "second system syndrome": designing a completely new system from scratch was difficult to develop and difficult to adopt. In contrast, 99DOTS started by building a narrow, high-functioning workflow for adherence that drew excitement and uptake from staff. As our software matured, it gradually came to replicate much of the functionality of the broader platform. Put differently, 99DOTS served as a kind of benevolent "trojan horse" that enabled long-sought upgrades in critical IT infrastructure.

While factors such as these can help to explain the enthusiasm that partner organizations have shown for 99DOTS, we are the first to recognize the gap between the scale of the system and the evidence for its purported benefits. We are working hard to close this gap and look forward to sharing more data in future papers.

## 8 GENERALIZING TO OTHER CONTEXTS

Many of the strengths, and also limitations, that we observed for 99DOTS are intimately dependent on the context that we studied.

In some respects, our deployment context offered the best-case scenario for 99DOTS. Focusing on tuberculosis, a disease which is unforgiving to non-adherence, has a precedent for monitoring adherence at nearly any cost (DOT), and is prevalent in lower-income populations (served by lower-resourced treatment programs) elevates the value proposition of 99DOTS. Our deployments thus far have focused on the public sector in India, which has several inherent characteristics that favor scalable implementation of 99DOTS. Perhaps most important are a centralized supply of standard-issue medications and a dedicated staff of health workers to follow up on adherence information. Our efforts to deploy 99DOTS in the private sector, while still ongoing, have proven significantly more challenging, in part because there is a diversity of medications, a decentralized supply chain, and a historical absence of ongoing treatment support, which leaves little motivation for patients to call 99DOTS. Recent public-private partnerships are addressing these challenges and may create new opportunities for 99DOTS.

At the same time, there is at least one important dimension in which our study context was not perfectly well-suited to 99DOTS, which is the difficulty that many patients faced in accessing mobile phones. Limited access to phones is at least partly (if not completely) to blame for the limited proportion of patients that demonstrated high adherence via calls alone. The implication for present-day India is that 99DOTS is only applicable to a subset of patients; managing all patients will require a "cafeteria" of alternate approaches [57], which may include 99DOTS, DOT and potentially other means of technology or peer support. We believe that one of the most important questions for future work is whether higher rates of mobile penetration (either in other countries, or potentially in future-day India) can enable 99DOTS to be a universal solution, or whether there are other barriers (such as technical literacy, forgetfulness, or unwillingness to call) that strongly mediate uptake by patients.

## 9 CONCLUSIONS

While technologies have been shown to improve medication adherence in rich countries, until now they have been too expensive for widespread use in developing regions. 99DOTS aims to preserve the benefits of prior approaches while reducing cost and implementation complexity. Its philosophy is to replace a fully automated solution (such as an electronic pillbox) with one that contains a manual human step (placing a phone call). In other words, by "undoing" automation, it might be possible to offer transformative affordability without sacrificing user acceptance.

Though 99DOTS has witnessed scalable uptake, it is too early to declare victory. A large number of staff and patients have invested energy into the system in hopes of improving health outcomes. Until we have rigorously demonstrated such benefits, the most important work is ahead of us. We thus view the uptake of 99DOTS less as a result than as an opportunity, and one that we feel privileged to pursue collaboratively with others from the research community.

## ACKNOWLEDGMENTS

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