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Leveraging technology to improve tuberculosis patient adherence: a comprehensive review

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ABSTRACT

Tuberculosis (TB) is a chronic disease that requires long-term treatment, generally for at least 6 to 9 months. Patients should follow the recommended treatment scheme regularly and completely. Poor adherence to treatment can cause patients to remain a source of infection for others. Patients with TB need additional support during treatment, in terms of information, motivation, and emotional support. Compliance monitoring helps ensure that patients take drugs according to a predetermined schedule. Comprehensive approach review method, careful selection of relevant data from various sources. This aims to provide overview of modern technology used to optimize the success of TB treatment. This paper aims to provide various methods that have existed in conventional and technology-enhanced approaches to monitoring and evaluating the treatment of TB patients. The existing studies only focus on making tools as a reminder to take medication but do not evaluate whether the drug is consumed. In addition, this paper describes prospective ideas involving advanced technology by using the internet of things (IoT)-based smart medicine bottle to accommodate the problem and become an effective communication solution in TB medication.

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1. INTRODUCTION

Tuberculosis (TB) is transmitted from humans to humans through the air through droplets or nucleus droplets (<5 microns) that come out when a person infected with pulmonary TB or laryngeal TB coughs, sneezes, or talks. The droplets, which are tiny particles 1 to 5 µm in diameter, can harbor 1-5 bacilli and survive in the air for up to 4 hours, which accounts for their highly infectious properties. Due to their extremely small size, these droplets can reach the alveolar spaces in the lungs, where the bacteria replicate and blocks phagosome-lysosome fusion, allowing replication within macrophages. Granulomas formed in response to limit the spread of bacteria. However, resistance causes granuloma necrosis which damages lung tissue. The most infectious case is transmission from patients with positive sputum examination results 3+, Figure 1 [1], [2].

In 2020, the World Health Organization (WHO) estimated that around 10 million people had active TB, including 1.1 million children, with 1.5 million deaths from the disease, and a quarter of the global population infected with *Mycobacterium tuberculosis* (MTB) [3]. A person is suspected of having pulmonary

TB when he suffers from a cough for more than 2 or 3 weeks with sputum production and weight loss. Respiratory symptoms include chest pain, hemoptysis or coughing up blood, and shortness of breath, while constitutional symptoms are fever, night sweats, tiredness, and loss of appetite. A special condition that rarely occurs in cases of TB is peritoneal tuberculosis (PTB) [4]. Because of its distinctive nature, PTB diagnosis does not use sputum examination but ultrasound and computed tomography (CT) abdomen.

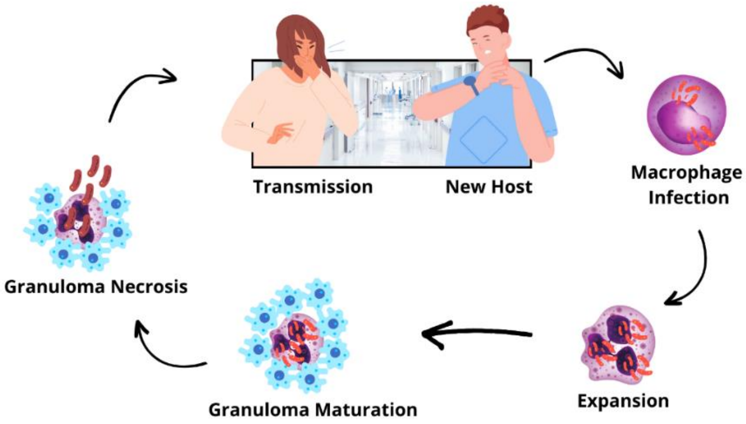

Figure 1. TB transmission pattern

In the last 100 years, the discovery of revolutionary anti-tuberculosis drugs (ATD), such as streptomycin, isoniazid, pyrazinamide, ethambutol, and rifampicin, together with combination drug treatment, have significantly improved global TB control. As ATD are widely used, multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of MTB have emerged due to acquired genetic mutations and posed a major problem for effective treatment [5]–[7]. Poor compliance was cited as the main cause reasons for suboptimal clinical benefits of TB treatment, and this leads to worse clinical outcomes, including disease progression drug resistance, increased duration of infectivity, and transmission to other people. TB control efforts have significant challenges in the form of monitoring TB therapy determine the success of TB treatment [8].

This study proposes an innovative advanced technologies, by integrating internet of things (IoT)-based smart medicine bottles, create systems that not only monitor drug adherence but also provide real-time data to healthcare providers. Unlike existing approaches that primarily focus on reminders, the proposed system actively tracks medication intake and provides actionable insights into patient adherence [7]. This technology enables healthcare professionals to remotely monitor treatment progress and intervene proactively, reducing the likelihood of drug resistance and improving clinical outcomes [8]. By bridging the gap between technology and medicine, this approach has the potential to revolutionize TB therapy monitoring, ensuring timely intervention and minimizing the risk of non-adherence and transmission of TB.

2. METHOD

This comprehensive review employs a systematic approach, selecting and analyzing relevant data from diverse sources to ensure thorough and reliable findings. The study focuses on presenting a detailed overview of modern technologies that enhance the effectiveness of TB treatment. By integrating extensive research and rigorous analysis, it highlights advancements in tools and methods to address challenges in TB management. The review aims to provide valuable insights into innovative approaches for optimizing TB treatment outcomes.

2.1. Diagnostics

Patients with a risk of TB (TB contacts, weight loss, fever, night sweats, and chronic cough >2 weeks) should undergo an initial screening to diagnose pulmonary TB by bacteriological examination. The examination consists of direct microbiological examination, culture test, and molecular rapid test. In limited facilities, clinical diagnosis is carried out after the administration of broad-spectrum antibiotic therapy (non-ATD and non-quinolones). When the sputum examination yields + results, the patient is diagnosed with TB [9], [10].

2.1.1. Thoracic photo

Chest X-ray is a clinical diagnostic method used for suspected TB cases when bacteriological test results are negative. It is a standard imaging technique that utilizes computer-aided detection (CAD) with X-rays to generate distinct lung images for TB diagnosis. Chest CT scans, whether performed with or without contrast, can provide more detailed insights into radiographic findings by distinguishing between active and inactive TB or detecting changes not visible on standard X-rays. Active TB is typically marked by features such as centrilobular nodules, tree-in-bud patterns, thick-walled cavities, consolidations, miliary nodules, pleural effusions, or necrotic lymphadenopathy. In contrast, inactive TB presents as stable alterations over six months, including scarring (peri-bronchial fibrosis, bronchiectasis, and architectural distortion) and nodular opacities like calcified granulomas and lymph nodes [9], [11].

2.1.2. Serological test

Diagnostic confirmation relies on serological tests like the interferon gamma release assay (IGRA), which functions similarly to the Mantoux test. Both tests aim to evaluate the frequency of the body's exposure to MTB. Another serological method is MMEC/AG-iELISA, designed to diagnose MTBC infections in multiple hosts, primarily caused by *M. bovis* and *M. tuberculosis*. This test is known for its high sensitivity and specificity. However, its implementation can be prohibitively expensive [10], [12].

2.1.3. Polymerase chain reaction test

Polymerase chain reaction (PCR) is a highly accurate molecular diagnostic method for detecting MTB and drug resistance, particularly to rifampicin. It offers rapid results within hours, unlike culture tests that require weeks [13]. GeneXpert MTB/RIF is the most widely used PCR-based test, identifying MTB and rifampicin resistance in a single run, making it essential for diagnosing MDR TB and extrapulmonary cases. PCR tests work with various samples, including sputum, pleural fluid, cerebrospinal fluid, and biopsy tissue. Despite its advantages, PCR is costly and may not distinguish between active and latent TB, as it only detects MTB DNA. Additionally, false-negative results can occur in samples with very low bacterial loads, necessitating complementary diagnostic methods for confirmation [14]–[17].

2.2. Duration of medication

TB patients in category I must comply with treatment for 6 months. The first phase includes two months of treatment using Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol [18]. The second phase is the continuation of phase one, wherein Isoniazid and Rifampicin should be given for the next 4 months. Adherence to this regimen is crucial to ensure the elimination of the bacteria and to prevent the development of drug resistance. Delays or interruptions in treatment can lead to treatment failure, prolonged infectivity, and the emergence of MDR TB [19]–[22].

2.3. Dosage and drug resistance

TB patients must adhere to the recommended dose of ATD based on their individual body weight. This dose range includes minimum and maximum limits to ensure the drug is effective in killing bacteria without causing toxicity or adverse side effects. Correct dosing is critical, as insufficient amounts can lead to ineffective treatment and drug resistance, while excessive doses can result in dangerous side effects. Monitoring the patient's weight during treatment is essential to adjust the dose and maintain optimal therapeutic results [18]. Comprehensive details on the dosage of TB drugs are displayed in Table 1.

Table 1. Dosage of TB drugs

Drugs	Daily dosage (mg/kg/day)	Dosage 2×/week	Dosage 3×/week
Isoniazid	5-15 (max 300 mg)	15-40 (max 900 mg)	15-40 (max 900 mg)
Rifampicin	10-20 (max 600mg)	10-20 (max 600mg)	10-20 (max 600mg)
Ethambutol	15-40 (max 2 grams)	50 (max 2.5 g)	15-25 (max 2.5 g)
Streptomycin	15-40 (max 1 gram)	25-40 (max 1.5 g)	25-40 (max 1.5 g)

Taking multiple TB drugs daily can be overwhelming for patients, especially when they are required to take four different medications. This complexity may lead to medication fatigue, reducing patient adherence to the prescribed regimen. Fixed-dose combination (FDC) therapy simplifies this process by combining all four drugs into a single pill, making it easier for patients to follow their treatment schedule. By reducing the pill burden, FDC therapy not only enhances patient adherence but also improves the likelihood of successful recovery and helps prevent the development of MDR TB [18], [23], [24].

2.4. The impact of non-adherence to tuberculosis therapy

Forgetting to take medication is very common, especially if the medication is taken for a prolonged period. The clinical management of MDR TB is complex. Patients who do not adhere to 1st line treatment will develop resistance. Therapeutic approaches and the prognosis of resistance patterns of second and third line ATD which are less efficacious, more toxic and more expensive than first line drugs. Of course, category II treatment will make the patient feel even more uncomfortable, because category II treatment also requires intramuscular medication (injection) every day [25].

2.5. Tuberculosis patients adherence monitoring method

Previously, TB therapy monitoring was directly observed. This became the standard procedure to ensure medication adherence by patients over long durations of treatment and monitor the side effects of the drug. Monitoring in TB treatment is very important because the bacteria can infect any organ such as the brain, bones, or kidneys, which can cause serious complications and even death. The chain of TB infection can be cut by regular treatment. Monitoring treatment can increase TB patient compliance in taking medication, which will have a major impact on improving the patient's quality of life [1]. The following sub-sections elaborate on several methods which have been developed for monitoring TB therapy.

2.5.1. Conventional method

The approach to improve medication adherence is represented by the intermittent regimen, the efficacy of which was demonstrated in 1964 in Chennai, India. The recurrence rate was 8% after 2 years of follow-up. Incentives and supports (e.g., money, food, incentives for transport) are important to improve adherence, especially in resource-limited countries. Poor patients living in rural areas can lose their jobs and daily wages due to medical visits in distant urban areas. As such, national TB programs should identify geographic areas or social groups where these nonmedical interventions can be important in increasing adherence. The level of patient adherence to treatment can be assessed by morisky medication adherence scale (MMAS -8), in which patients are asked to answer 8 questions through a questionnaire. The level of compliance can be categorized into high (8 points), moderate (6/7 points), and low (<6 points) [26], [27]. Systematic review in China found that only 50% of TB patients received directly observed therapy (DOT) (20% from health workers and 30% from family members), and 50% self-administrated medication (SAT) without any medication adherence support [24].

2.5.2. Short message service-based method

Short message service (SMS) methods have been adopted by several developing countries due to their low cost and widespread network availability. For example, in Africa, sending SMS reminders to newly diagnosed TB patients have been shown to increase the urgency to start treatment. Patients who received SMS reminders to take their medication showed higher adherence compared to those who did not receive reminders [28]. In Uganda, a similar approach was used, where patients received automated SMS reminders daily to confirm whether they had taken their medication, leading to improved treatment outcomes [29]. In addition, SMS reminders were sent to registered relatives of patients if the patient failed to respond within the specified time, ensuring that there was ongoing monitoring of patient adherence. Although SMS reminders did not significantly impact treatment completion or overall adherence, they represent a technological intervention that supports treatment adherence and contributes to improved patient outcomes [30], [31].

2.5.3. Internet of things-based drug monitoring system

IoT supports healthcare systems and enables more responsive monitoring and decision-making through real-time data acquisition from multiple resources [32]. The IoT revolution aids in developing an advanced system of healthcare that is much more personalized and effective in diagnosing patients easily. IoT in patient care does a great job of storing and processing large volumes of patient clinical records, including data from sensors for healthcare analytics [33], [34]. The application of IoT in the health sector aims to improve a person's quality of life by integrating technology and medical services, can overcome the limitations associated with traditional networks [35]–[37]. IoT in the medical field has been used for biomedical and health monitoring general patient diagnosis system such as reporting heartbeat rate, pulse, blood pressure (BP), temperature and activities of the patient using various smart sensors with more accuracy [38]–[40].

2.5.4. Web-based applications and smartphone applications

TB infection requires extensive treatment. One strategy that can be used to help adherence to latent tuberculosis infection (LTI) treatment is to use an application for mobile devices (such as smartphones and tablets). The use of technology in healthcare can assist in avoiding inappropriate treatment, enable monitoring of treatment by healthcare professionals, and support patients to complete treatment [41]. WHO recommends the use of mobile health (mHealth) technology as an emerging opportunity to close the gap in TB care through increased public private mix (PPM). mHealth in PPM for monitoring and treating TB can be carried out through; i) TB screening, ii) TB case notification, iii) TB treatment adherence, iv) data collection and management, v) patient referral and follow-up, and vi) education. However, the evaluation of whether mHealth improves adherence to therapy has not been studied [42].

2.5.5. Video calls

Video directly observed therapy (vDOT) has emerged as an effective intervention for monitoring TB medication adherence remotely. It uses video calls to allow health workers to observe patients taking their medications in real time, ensuring appropriate intake without the need for in-person home visits. The use of vDOT offers the advantage of monitoring multiple patients simultaneously, increasing efficiency and reducing the risk of TB transmission in crowded health facilities. As demonstrated by studies in Uganda and Vietnam, Internet connectivity is a challenge. vDOT is a promising digital tool in TB care that improves patient monitoring and treatment completion [37].

2.5.6. Drones

Drones are emerging as a transformative tool in healthcare, particularly in the delivery of medical supplies to remote or hard-to-reach areas such as medicines, vaccines, and diagnostic samples. With real-time tracking capabilities, drones ensure the safety and accuracy of medical deliveries, reducing the risk of loss or delay. In TB care, drones can play a critical role in delivering ATD to patients in remote areas, ensuring timely access to treatment. This can improve adherence to TB therapy. The integration of drones into healthcare systems can revolutionize the efficiency and accessibility of therapy than the existing conventional method [43]–[45]. Data on medication reminder methods are summarized in Table 2.

Table 2. Summary of medication reminder methods

Reminder types	Storing medicine	Understanding TB	Medication reminder	Daily data	Reminder when forgot to take medicine
Conventional method assessed by Morisky medication adherence scale (MMAS)-8, in which patients are asked to answer 8 questions through a questionnaire [26].	-	-	-	-	
SMS reminders to improve adherence and cure of TB patients [28].	-	-	√	√	-
IoT-based drug monitoring system [34], [39], [40], [46].	-	-	√	√	√
Web-based applications and smartphone applications [42].					
Direct observation with video call smartphone-enabled video-observed treatment for TB [37], [47].	-	-	√	-	√
Drone for efficiency to deliver medical services [43]–[45].	-	-	-	-	-
Smart medicine bottle for monitoring and evaluation of TB patient treatment compliance.	√	√	√	√	√

Smart medicine bottle is superior because has a function to store medicine supplies, which is equipped with sensor technology so that it automatically records every time medicine is taken. Ensuring that drug use data is recorded accurately without requiring manual input from the patient. Provide warnings and reminders to take medication repeatedly, if the patient forgets not to take the medication on a predetermined schedule. Providing an understanding of TB is better because knowledge is closely related to higher levels of recovery. Ease of using the smart medicine bottle, so smart medicine bottle can be used by all patients. These tools enable direct communication between health workers, patients, and their families, with updates and reminders delivered through apps, ensuring continuous and efficient engagement. Frameworks for TB monitoring and adherence evaluation mention in Figure 2: conventional monitoring involves face-to-face interactions where doctors or nurses visit TB patients or patients travel to healthcare facilities for evaluations. SMS-based monitoring utilizes text messages to provide reminders and consultations. Messages are sent through a hospital-linked SMS gateway, involving both patients and their families to support medication adherence and home care. Mobile app and social media monitoring leverages mobile applications and social media platforms for a more interactive approach.

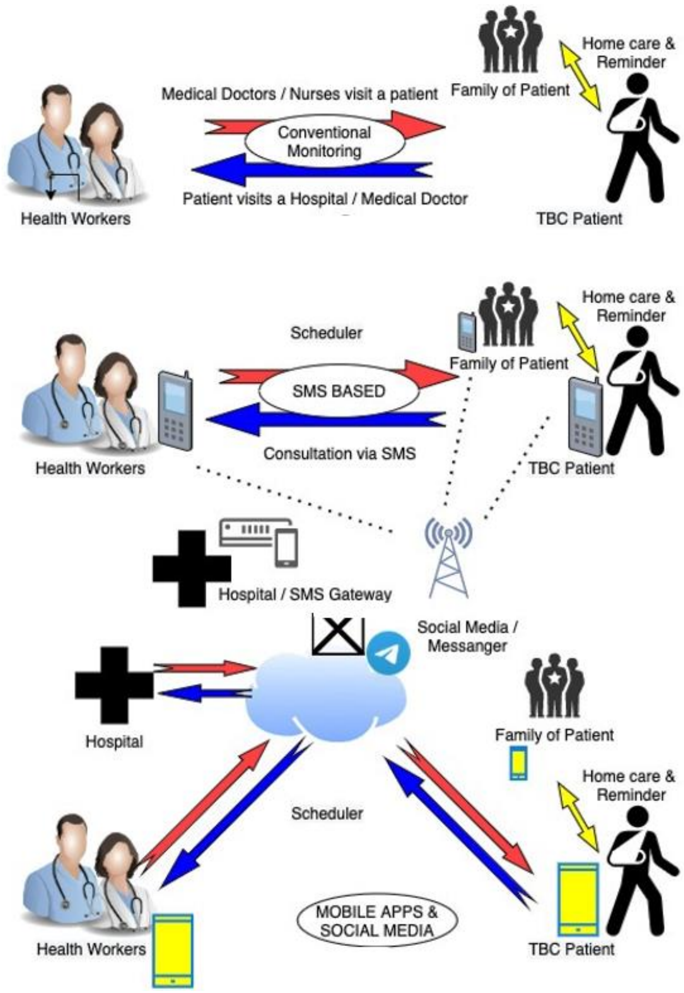

Figure 2. Frameworks for TB monitoring and adherence evaluation

An integrated approach through the application of technology between health services and the community, especially TB patients, as a method for monitoring TB therapy is very necessary. Assessing the fulfillment of the MMAS-8 questionnaire, reminders via SMS, applications/smartphones in the form of medication reminder alarms, video calls every time, have been implemented, but this technology is limited to one-way communication, namely health energy provides reminders to take medication to patients/patients' families, without knowing of contrary reports from patients [19]–[22]. IoT-based smart medicine bottle develops the direction of communication between health workers and patients from one-way communication to two-way communication. For the purpose of keep connection to the health status of patients with TB, health services remind patients about medication, patients take medication and information related to patient will reach to health workers in real time. This will improve the quality, efficiency and accessibility of health services [33].

2.6. Challenges related to tuberculosis control

A significant challenge for TB control efforts is adherence to taking medication schedules, monitoring and determine the success of TB treatment. However, for many patients who live in remote and hard-to-reach areas, the public stigma against TB as a shameful disease makes them reluctant to get checked or undergo treatment, which possible exacerbating the spread. Contact tracing is difficult, high poverty makes access to good nutrition limited, crowded environments, such as slums make TB spread faster. Another challenge is a lack of TB knowledge, which hinders early detection and treatment adherence. Limited funds in countries with a high TB burden, especially for providing medicines and monitoring medication taking until the patient complete from treatment and cured [48].

3. RESULTS AND DISCUSSION

This writing aims to improve treatment adherence of TB patients by developing a technology-enhanced system. One example is IoT based-smart medicine bottle, an Android-assisted tool to store medicine. This bottle contains TB drugs and informs the patients when to take the medicine. A weight sensor attached to the bottle will detect the reduction in weight as an indication of the patient taking the medicine and send the report to the health worker. Reduced weight will also send a notification to the patient's smartphone. Likewise, if the patient has yet to take the medicine on schedule, the health worker will receive notification. Smart medicine bottle will be powered by batteries to operate the sensor. A microcontroller and a solar cell can also be installed to ensure sufficient power for the tool. The bottle will be filled with ATD which the patient must take every day.

A smartphone can also be equipped with a TB medication monitoring system in the form of an internet-based application. This application can provide information to health workers regarding patient’s medication adherence. Doctors can monitor treatment without going directly to the patient's house. This will certainly be very effective in that it reduces the risk of transmission due to exposure to MT. When a TB patient has not taken the medicine, the system can notify the health worker and then the worker will send a notification accordingly. This mechanism is effective in reminding the patient to take the medicine. Mechanism of smart medicine bottle mention in Figure 3.

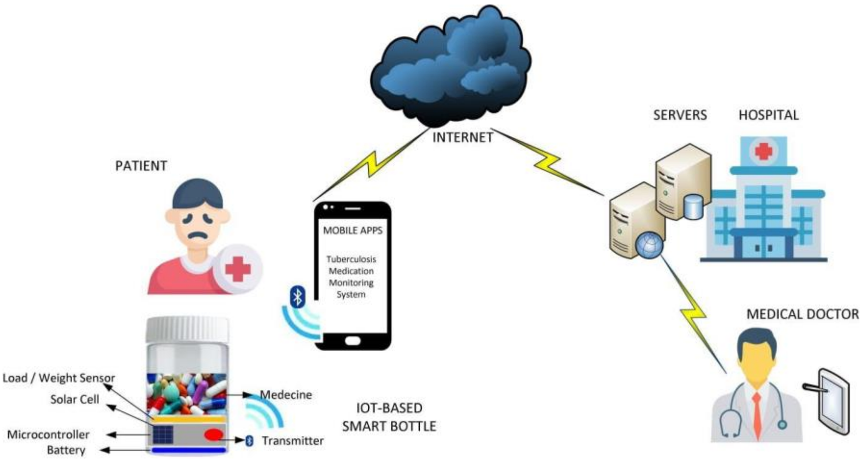

Figure 3. Mechanism of smart medicine bottle

Smart medicine bottle uses general IoT architecture in the form of a perception layer, network layer, and application layer. The perception layer contains sensors that collect real-time data from the environment needed for further monitoring. This layer consists of controllers, sensors, actuators, and RFID tags. The network layer functions as a mediator to transfer information from the perception layer to other network components. As the top layer, the application layer enables health workers to retrieve information and further perform data analysis as the basis for sending reminders to patients. Notwithstanding, using IoT is not without challenges. Due to the heterogeneity of treatments and monitoring mechanisms and the required comprehensive service throughout the network, it requires attention to the security of data collection and processing [6].

IoT-based smart medicine bottles have become one of the most growing research areas in the field of biomedical engineering [49]. The research discussed in tele-medicine systems covers the field of health services and monitoring systems especially for remote patients [50]. Tele-medicine systems can be used to address patient concerns and complaints in real-time [51]. Tele-monitoring healthcare systems, which are one type of tele-medicine system, have been used to monitor patient health status from a distance, such as home or office. This is done using various information and communication technology application [52], [53]. Monitoring TB patient in healthcare systems not only have a positive impact on patients' health status and their quality of life, but also have a positive economic impact on patients and society at large [53], [54].

4. CONCLUSION

TB has high mortality and morbidity rates; therefore, serious intervention is needed in treating and monitoring patients, especially in terms of medication adherence reminders. Existing technology has proven effective in supporting compliance through reminders and notifications, but still has several weaknesses, such as timeliness of reporting, exposure to bacteria, cost. Smart medicine bottle can work automatically to send daily reports of patient medication consumption and is easy to use. This is very useful for health workers to ensure that intervention can be carried out immediately if the patient does not regularly take medication. This is expected to increase treatment compliance and increase the cure rate for TB patients as well as being an effective communication solution.

Technology helps increase the success of treatment, from making diagnoses and evaluating treatment progress to reminding patients to take medication. Research developing tools to remind patients to take medications regularly has not evaluated the effectiveness of the proposed mechanisms. Previous researchers only focused on creating tools to tell patients to take medication but did not evaluate whether the medication was consumed. Further evaluation needs to consider the cure rate within a period as an accurate indicator of the success of technology integration in monitoring and treating TB patients.

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C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

INFORMED CONSENT

We have obtained informed consent from all individuals included in this study.

ETHICAL APPROVAL

This paper does not discuss the use of humans or animals.

DATA AVAILABILITY

Data availability is not applicable to this paper as no new data were created or analyzed in this study.

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