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MORALITY BEFORE KNOWLEDGE

The potential of ingestible sensors combined with family involvement interventions for medication supervision in Tuberculosis patients: A literature review

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ABSTRACT

Background: Tuberculosis (TB) is an airborne infectious disease that remains the second leading cause of death from infectious diseases globally. A major challenge in eliminating TB, despite it being preventable and curable, is the low adherence to treatment. This literature review aims to provide insights into the potential of ingestible sensors combined with family involvement interventions for medication supervision in TB patients, ensuring that medications are actually swallowed and addressing a key limitation of the previous DOT method. **Methods:** This study used a literature review method with the keywords "family engagement intervention", "digestible sensor", and "tuberculosis [MeSH]" to search databases such as Google Scholar, Science Direct, ResearchGate, and NCBI. Inclusion criteria included in vitro and in vivo experimental studies, cohort studies, comparative analysis studies, and reviews published in the last 10 years. Exclusion criteria included incomplete studies, inaccessible papers, and non-English/Indonesian texts. After applying these criteria, 35 journals and 1 book were selected for review and analysis. **Findings:** Ingestible sensors have shown over 80% effectiveness in monitoring medication adherence by providing real-time data for precise treatment adjustments. When combined with family involvement, these interventions address psychosocial barriers like stigma and lack of support, further improving adherence. This synergy significantly reduces non-compliance, prevents drug resistance, and enhances treatment outcomes for TB patients. **Conclusion:** Ingestible sensors combined with family involvement offer a more effective approach to TB treatment by ensuring medication is swallowed and providing psychosocial support, reducing risks of transmission, relapse, and drug resistance. However, equitable access and adequate infrastructure, supported by government and societal cooperation, are crucial for the successful implementation of this system globally. **Novelty/Originality of this article:** This study explores the innovative use of ingestible sensors combined with family involvement to improve TB treatment adherence, offering a novel contribution to TB management.

KEYWORDS: family involvement intervention; ingestible sensor; Tuberculosis [MeSH].

1. Introduction

Tuberculosis (TB) is an infectious disease that spreads easily through the air. To date, TB remains the second highest contributor to deaths caused by infectious diseases worldwide. According to data from the World Health Organization (WHO) in 2022, an estimated 10.6 million people globally were living with TB, and 1.3 million died from the

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disease. In Indonesia alone, more than 724,000 cases of TB were reported in 2022, increasing to 809,000 cases the following year (Ministry of Health of the Republic of Indonesia, 2024). Currently, Indonesia ranks second globally for the highest number of TB cases, primarily due to late diagnosis and low treatment adherence among active TB patients (WHO, 2024).

One of the main challenges in eliminating TB, a disease that is fundamentally preventable and curable, is the low level of treatment adherence among patients. This issue is largely influenced by the lengthy treatment process and the lack of adequate supervision and support. Based on global data from 2022, approximately 4.2 million TB cases went undiagnosed, and only 55% of diagnosed cases adhered to their treatment regimens. Non-compliance with treatment can lead to active transmission, treatment failure, or resistance to anti-TB drugs. Addressing drug-resistant TB requires costlier treatments and stricter monitoring, further increasing the economic burden on affected countries while also reducing the productivity of individuals suffering from TB (WHO, 2024).

Ending the TB epidemic is one of the global health targets included in the Sustainable Development Goals (SDGs) for 2030 under Goal 3 (Good Health and Well-Being). Indonesia has also set a target to eliminate TB by 2030 through its National TB Control Strategy (Ministry of Health of the Republic of Indonesia, 2020). To achieve this goal, it is essential to involve students as agents of change, utilizing technological innovations to accelerate the eradication of TB and other infectious diseases in Indonesia by 2030.

2. Methods

The method used in writing this literature review is a literature review using the keywords "family involvement intervention", “ingestible sensor”, and “tuberculosis [MeSH]”. The literature search was carried out using search engines such as Google Scholar, Science Direct, ResearchGate, and NCBI. The inclusion criteria for this literature search were in vitro and in vivo experimental research journals, cohort studies, comparative comparative analysis studies, and review studies with publication requirements within the last 10 years.

The exclusion criteria used were studies that had not been completed at the time of the literature search, studies that could not be accessed in full paper, and studies that used languages other than English and Indonesian. From the results of the literature search, the evaluation of inclusion and exclusion criteria was carried out by assessing the title and abstract as a first step, and then the full text was reviewed to see if there was a correlation between keywords in the journal so that it could support writing descriptions or analysis in this literature review. From the results of a literature search using inclusion and exclusion criteria, 35 journals and 1 book were obtained, which were used in this work.

3. Results and Discussion

3.1. About Tuberculosis

TB is an infectious disease caused by Mycobacterium TB (M.tb). This bacteria is classified as an acid-fast bacillus (AFB) because its wall structure has a high lipid content. This bacteria (<5 μm) is transmitted through the air via droplet nuclei. Droplets will be suspended in the air, especially in poorly ventilated rooms (Coleman et al., 2022). This transmission mechanism is what underlies the importance of rapid diagnostics and appropriate treatment to break the chain of spread of infection.

According to data from the World Health Organization, in 2023, TB will rank second in deaths from infectious diseases worldwide. Not only that, WHO also reported that of the 10.8 million diagnosed cases, only 55% of them were treated obediently. This is what causes the current number of TB cases to continue to increase, including treatment-resistant TB (WHO, 2024).

Most M.tb infections attack the lung parenchyma, but not infrequently also attack other organs such as bones, skin, and lymph nodes which are also called extrapulmonary TB. Several groups of people who have a high risk of contracting M.tb infection are: (1) HIV-positive people and other immunocompromising diseases; (2) people who take immunosuppressant drugs for a long period; (3) smokers; (4) high alcohol consumption; (5) elderly; (6) malnutrition; (7) having close contact with an infectious person with active Tuberculosis disease; (8) health workers; (9) poverty. Individuals who experience active infection from M.tb., can show symptoms including: (1) fever; (2) cough/coughing up blood; (3) shortness of breath; (4) chest pain; (5) malaise (Adinda Nezma Meidina et al., 2024).

3.2. Pathogenesis of Tuberculosis

Droplet nuclei from TB patients can enter the respiratory tract until they reach the respiratory bronchioles and alveoli of other people who interact with them. When M.tb enters together with droplets, alveolar macrophages will be activated and phagocytose M.tb. Whether or not a person is infected will depend on the quantity of bacteria and the quality of the body's immune system (Alsayed & Gunosewoyo, 2023). The pathophysiological and transmission scheme of TB can be seen in Figure 1.

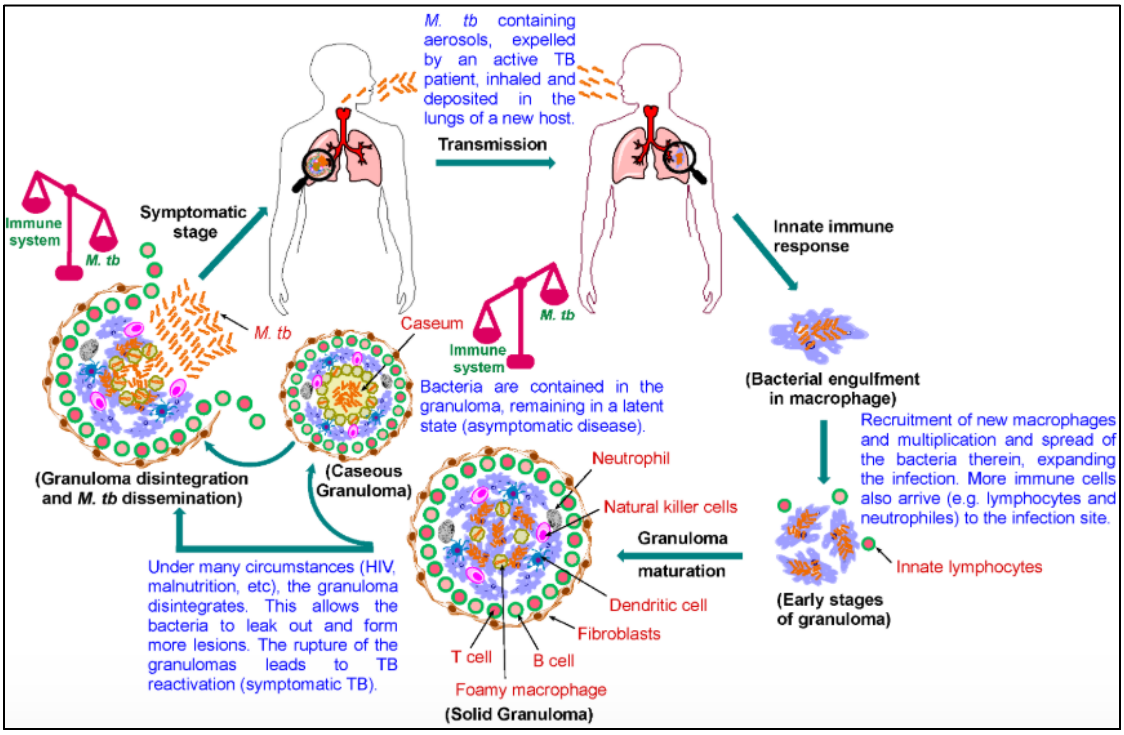

Fig. 1. Pathophysiology and transmission of TB
(Alsayed & Gunosewoyo, 2023)

Although the body naturally has a defense against contaminants that enter the body, including M.tb, this bacteria has the ability to hide and reproduce intracellularly in macrophages. If the macrophages die, the bacteria will exit the alveolar macrophages and spread the infection to monocytes and interstitial macrophages (Anastasiia Diatlova et al., 2023). In response to this, the body responds again by forming granulomas around the area of infection with the aim of forming a defense against the spread of M.tb. This process will cause lesions called primary focus as an early sign of TB infection. Unfortunately, M.tb can still survive in the granuloma by blocking phagolysosome fusion and subverting the immune response. At this stage, infected patients do not show typical clinical symptoms and are not contagious (Alsayed & Gunosewoyo, 2023).

The M.tb cell wall is composed of mycolic acid as its main component which plays a role in the formation of foam-macrophages. In addition, M.tb can interfere with the regulation of the body's lipid metabolism which causes disruption of the entry and exit of lipid particles. Both of these will induce the formation of caseous necrosis which will later soften in the final phase so that TB bacteria resuscitation occurs which causes the patient's infection to become active. M.tb will then be more active in spreading inflammation throughout the body (Alsayed & Gunosewoyo, 2023).

3.3. Tuberculosis treatment

Not all TB germ infections result in disease. Therefore, dormant TB and active TB disease are two diseases related to TB. Both active and inactive TB disease can be treated. Inactive TB disease can at any time turn into active TB disease, even if you don't feel sick. Caring for your inactive TB is the strongest defense against developing active TB disease. You may receive treatment if you have active TB. Because of their strength, TB bacteria may take a long time to die. It is very important to take and complete all TB medications as recommended by your doctor (Centers for Disease Control and Prevention, 2024). Antibiotics should be used for at least six months as part of standard treatment for culture-positive TB. Shorter and more efficient TB treatment allows for faster recovery and improves the patient's quality of life (Carr et al., 2022).

When treating patients aged 12 years or older who weigh 40 kg or more and have pulmonary TB caused by an unknown or suspected drug-resistant organism and have no contraindications to this regimen, Centers for Disease Control and Prevention (CDC) recommends RPT-MOX Regimen 4 month. Eight weeks of daily treatment with RPT, MOX, INH, and PZA constituted the intensive phase of a four-month daily treatment regimen. Nine weeks of daily treatment with RPT, MOX, and INH is the continuation phase. For a total of 119 treatment doses, the anti-TB medication should be taken once daily with meals, seven days a week. As with a typical 6-month regimen, at least five of the seven weekly doses should be given under close supervision. If there are no other known drug interactions between antiTB drugs and antiretroviral drugs, people with HIV who have a CD4 count ≥100 cells/μL and are currently taking efavirenz or intend to start taking it as part of their antiretroviral therapy (ART) regimen can take efavirenz. 4 month regimen (Carr et al., 2022). The following patient populations are not recommended to follow this regimen by the CDC: Patients with a history of prolonged QT syndrome or concomitant use of one or more QT prolonging medications (other than MOX); patients taking medications with known clinically relevant drug-drug interactions with RPT, MOX, INH, or PZA; patients with initial isolates of Mycobacterium TB known or suspected to be resistant to INH, PZA, rifampicin (RIF), or fluoroquinolones; body weight<40 kg; age<12 years; pregnant or breastfeeding; most types of suspected or documented extrapulmonary TB infection (Carr et al., 2022).

3.3. TB drug use monitoring

3.3.1. Directly observed therapy (DOT)

Without a rigorous commitment to long-term treatment for TB, it is now widely recognized that the disease can worsen, patients can continue to spread, and mutations that make the bacteria resistant to therapy can occur. Drug-resistant TB (DR-TB) requires a longer treatment plan, more expensive drugs, is less effective, and is often associated with increased mortality. Additionally, DR-TB strains can spread, rendering affected treatments ineffective in new patients. Directly observed therapy (DOT) was developed as a result of research conducted in Madras and Hong Kong that emphasized the importance of strong adherence for effective treatment outcomes. Characteristics of sufferers such as poverty and low education have been known to reduce compliance with TB treatment since 1964. Sumartojo added, depending on the disease being treated, compliance with treatment can vary from person to person. Since adherence to treatment is influenced by individual, societal, and structural factors, it is clear that tailored support systems are needed to improve the effectiveness of TB treatment (Garfein and Doshi, 2019).

DOT is recommended as standard therapy in the 2016 US clinical practice recommendations for the treatment of TB. A health care professional watches the patient take his or her medication, watches for side effects, and offers social support (e.g., personal contact, encouragement, advice, or assistance in negotiating problems resulting from the disease) in the Department of Transportation. Although attending a DOT in person can be logistically difficult, this usually requires an in-person meeting at a mutually agreed location in the community or clinical setting. Arranging transportation for a DOT may be difficult, and scheduling may conflict with the patient's work, education, or other daily activities. The daily influx and outflow of medical personnel can also raise unwanted questions from neighbors or co-workers or cause patients to be stigmatized in the case of community-based DOT. Additionally, in-person DOT may not always be possible in the event of a pandemic, natural disaster, or severe weather (Mangan, 2023). To improve adherence support, patient-centered strategies are needed, ideally taking into account the patient's daily routine, travel needs, and treatment costs. It is important to develop new treatment support strategies that maintain patients' sense of agency while lowering health care costs and meeting the level of trust offered by the DOT (Garfein and Doshi, 2019).

3.3.2. Live video observation therapy (vDOT)

Live video observation therapy (vDOT) is a form of electronic DOT (eDOT) that uses the same concepts as DOT. It uses video-enabled devices (such as computers, tablets, or smartphones) to monitor TB treatment. TB programs can use vDOT to watch patients take TB medication by watching live (synchronous) or recorded (asynchronous) video. When they receive TB treatment, this can give patients more freedom and flexibility, thereby increasing patient satisfaction (Centers for Disease Control and Prevention, 2023).A patient who ingests TB medication outside of regular clinic hours, such as on weekends, holidays, or evenings, can be observed by the TB program thanks to vDOT recording. Patients can register themselves as taking TB medication, depending on the program. When patients have an internet connection, they can send the recordings to the TB program. Because TB programs can allow patients to take TB medications while traveling, vDOT directly offers flexibility (Centers for Disease Control and Prevention, 2023).

In most locations that use traditional face-to-face DOT, TB programs can use vDOT as part of patient case management. Among them are (1) HIV patients; (2) children and adolescents who receive assistance from parents or guardians; (3) individuals in rural areas; (4) patients in institutions, provided that the regulations governing those institutions respect patient privacy and allow the use of electronic devices (Centers for Disease Control and Prevention, 2024). To track TB therapy, TB programs must continue to have the capability and availability of face-to-face DOT. The best option may be in-person DOT for (1) patients who are prescribed injectable drugs; (2) individuals who require thorough clinical supervision due to their medical fragility; (3) people who do not comply with vDOT treatment; (4) along with those who prefer to earn DOT directly (Centers for Disease Control and Prevention, 2024).

If TB patients or their daily caregivers cannot use vDOT, do not do so (1) clearly communicate or demonstrate that you are comfortable or; (2) proficient using the vDOT platform (Centers for Disease Control and Prevention, 2024). Use caution and clinical judgment when treating patients who have (1) previously experienced TB treatment side effects; (2) drug resistance, or; (3) treatment failure or poor compliance (e.g., patients with cognitive impairment, psychiatric illness, or a history of noncompliance) (Centers for Disease Control and Prevention, 2024). TB programs should provide instructions to patients on how to download and utilize vDOT technology at the start of the program. Before the session begins, patients can learn the vDOT protocol through patient education and practice sessions. The teach-back technique can be used to verify whether the patient understands vDOT during patient education. TB programs should consider providing vDOT training during face-to-face DOT sessions if patients begin using DOT and transition to vDOT (Centers for Disease Control and Prevention, 2024). The following topics should be discussed in education sessions with patients: (1) potential out-of-pocket costs (such as patient mobile data plans and usage fees); (2) situations that result in discontinuing vDOT and switching to face-to-face DOT (Centers for Disease Control and Prevention, 2023).

3.4. Challenges of Tuberculosis treatment and care

The treatment and care of TB often present significant obstacles to successful patient recovery, hindering progress toward the goal of TB elimination by 2025. Current TB therapies are time-intensive, involve medications that can cause harmful side effects, and require strict patient adherence. Non-compliance with treatment is a widespread issue, influenced by numerous factors. As a result, there is an urgent need to enhance TB management through improved testing, treatment, and patient education. These efforts are crucial for achieving the target of eliminating TB by 2050 and alleviating the global burden of the disease (Matteelli & Alffenaar, 2022). Innovative technologies, such as ingestible sensors, offer promising solutions to enhance patient adherence to TB therapy.

Several factors, both internal and external, can influence TB treatment and care. Internally, a key factor is patient adherence to the prescribed treatment regimen. When patients fail to follow their treatment plan, it can lead to drug resistance, which is a significant obstacle in managing TB. The treatment process itself is lengthy and complex, typically lasting six months or more, with multiple medications involved. This can overwhelm patients, creating a sense of burden that may eventually lead them to discontinue treatment. Additionally, the side effects of TB treatment can cause discomfort, forgetfulness, and a reluctance to continue therapy. These negative experiences often trigger non-compliance, as patients may stop taking their medication to avoid the unpleasant effects.

Another contributing factor to non-compliance is a lack of education and awareness. Many patients underestimate the importance of adhering to the treatment regimen, largely due to a limited understanding of the potential consequences of non-compliance, such as the development of drug-resistant TB. This gap in knowledge, commitment, and understanding can hinder effective treatment. Educational interventions are crucial in improving patient adherence to TB treatment and care (Grace Florita Pasaribu et al., 2023).

In addition to internal challenges in the TB treatment and care process, external factors also play a crucial role in the rehabilitation of TB patients. Many TB patients experience social discrimination, as the surrounding community often perceives TB as a contagious disease. This misunderstanding can lead to stigmatization and social exclusion. The resulting discrimination can exacerbate feelings of isolation and potentially lead to depression, negatively impacting the patient's quality of life (Fuady et al., 2024). This stigma may prevent patients from seeking treatment or adhering to their prescribed regimen. The feelings of discrimination, loneliness, and insecurity associated with stigma can be significant barriers to effective treatment and care (Aranas et al., 2023). Stigmatization can severely hinder efforts to control and manage TB.

Psychosocial support is a key external factor in supporting TB patients (Thomas & Stephen, 2020). Additionally, having a strong support system plays an essential role in the rehabilitation process. For instance, the presence of supportive family members or community health workers, such as Medication Supervisors (PMOs), can greatly improve treatment adherence. Unfortunately, the persistent stigma in many communities can leave TB patients without the necessary support from family, friends, or their broader environment. This lack of support is one of the significant challenges that complicates the treatment process for TB patients.

Addressing the challenges in TB treatment and care requires fostering innovation in therapy management. Effective interventions are crucial to ensure patient adherence to treatment. Therefore, evaluating new technologies, such as ingestible sensors, is necessary to enhance adherence and overcome obstacles to TB rehabilitation. These innovations can significantly improve treatment outcomes and contribute to the goal of eliminating TB by 2050 (Matteelli & Alffenaar, 2022).

3.5. Ingestible sensor

3.5.1. Concept of ingestible sensor

Ingestion sensors, also known as "digital pills," are unique, swallowable gadgets that monitor and transmit physiological data from within the gastrointestinal tract. These sensors provide a non-invasive technique to monitor internal health because they are designed to pass through the digestive system and collect real-time data on a range of health markers. Ingestible sensors are usually protected from the severe GI tract environment by biocompatible capsules that contain the internal electronic components (Chai et al., 2021). Materials that are frequently available in food supplies are used to create the ingestible sensor (Alipour et al., 2020). Like dietary fiber, it contains trace levels of silicon, copper, and magnesium that are absorbed by the body (Chai et al., 2021). The radio frequency emitter is coated with food-safe epoxy to prevent metal from leaking. It passes through the digestive system and is expelled as feces (Chai et al., 2021). See the figure 2. to understand about the prototype model of ingestible sensor.

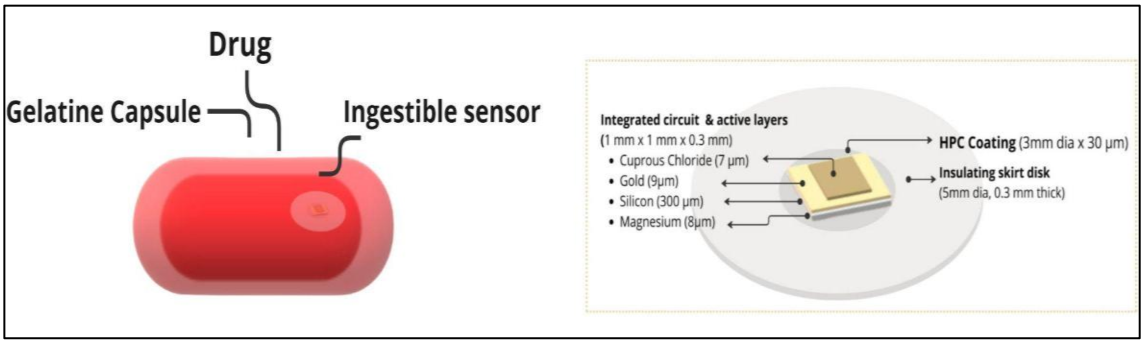

Fig. 2. Ingestible sensor specification.
(Hafezi et al., 2015)

Digital ills are formulated from drugs embedded with a sensor that can be swallowed and encapsulated into a gelatin capsule. The sensor consists of an active layer, integrated circuit, and insulating skirt disk. The active layer is composed of a thin layer of magnesium (Mg), copper (Cu), and chloride (Cl) which later when interacting with physiological gastric fluid will produce a battery that activates the skin patch. Under this layer is a thin layer of gold that functions as a current collector and an integrated circuit and insulating skirt disk made of cellulose food particles that strengthen the electric field of the sensor.

The amount of material used is lower than the recommended intake limit, making the sensor safe for consumption even in the long term (Hafezi et al., 2015). These passive pills activate upon contact with acidic electrolytes in the stomach, transmitting signals to a wearable reading device outside the body, where the data is recorded and monitored (De la Paz et al., 2022). See the Figure 1. to understand about the work flow of ingestible sensor. Within one to two minutes of ingestion, the reader device saves the date, time, and sensor ID and sends the data to a cloud server for real-time adherence information (Alipour et al., 2020). Due to the increasing availability of smartphones with internet connectivity, both users and doctors can easily monitor and evaluate data generated by ingestible sensor technology online. This accessibility significantly reduces the costs associated with conventional methods, such as DOT or VDOT, as it minimizes the need for in-person monitoring while maintaining effective adherence tracking.

The proposed Ingestible sensor with family involvement workflow is as shown in the figure above. The clinician will provide a medicine bottle containing anti-TB drugs with a sensor that can be swallowed that has been dosed to be consumed for 1 month for the patient. Each medicine bottle and each drug inside it has been fitted with a sensor with the same numeric code. The code will be inputted by the clinician into his/her mobile application. Furthermore, the clinician will also connect the patient's data with the patient's application and one of the family members registered in the application. In addition, at the first meeting, the patient will also receive a medicine bottle cap that has an alarm to remind the patient to take the medicine, but this medicine bottle cap will only be received by the patient once during treatment. The patient will pick up the medicine package again after one month (Hafezi et al., 2015).

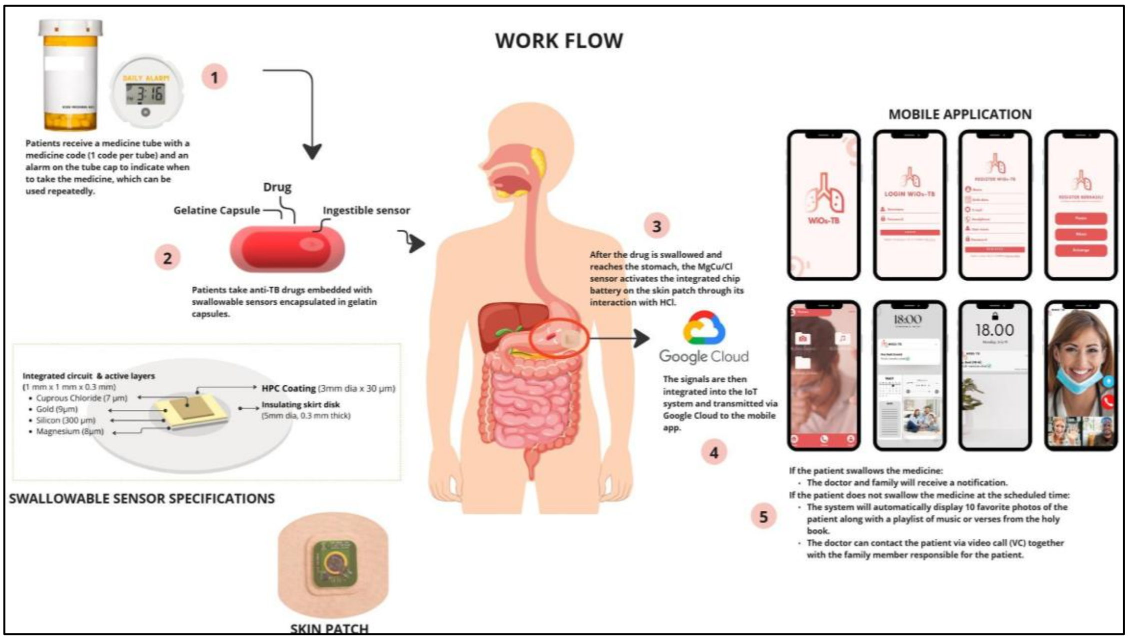

Fig. 3. Ingestible sensor workflow
(Hafezi et al., 2015)

3.5.2. Effectiveness of ingestible sensor

In 2015, the FDA approved the first ingestible sensor technology, and in 2019, it approved a second sensor version. This technique tracks oral medication adherence. The capacity of these medical devices to record remote, real-time data on medication ingestion. These novel digital technologies may offer ongoing treatment adherence support as well as precise oral dose ingestion confirmation (Manjula et al., 2024).

Ingestible sensor technology has shown significant promise in enhancing medication adherence for various medical conditions by providing real-time data on medication intake (Chai et al., 2021). Adherence to prescribed medication regimens is crucial for the successful treatment of diseases such as hypertension, mental health disorders, TB, and organ transplantation (Aremu et al., 2022; Liu et al., 2022). Ingestible sensors provide precise data on medication intake, enabling healthcare providers to swiftly adjust treatment plans. By integrating adherence data with AI algorithms, patients benefit from personalized reminders and behavioral insights, promoting better compliance and improving overall health outcomes. Research has demonstrated the effectiveness of this technology, with studies indicating notable reductions in blood pressure, LDL cholesterol, and HbA1c levels, as well as medication adherence rates exceeding 80% (Alipour et al., 2020).

In Liu's study, ingestible sensors were shown to significantly improve adherence to antiretroviral therapy (ART) in HIV patients, demonstrating high acceptance and effectiveness in sustaining adherence through real-time monitoring and mobile app reminders (Liu et al., 2022). The 2021 human factors validation study of the ID-Cap System also supported its usability, with 97.5% of scenarios successfully completed by participants, emphasizing its potential to improve drug adherence in transplant recipients (Baumgartner et al., 2021). In addition, ingestible sensors have proven effective in pilot studies for TB, are being explored for HIV pre-exposure prophylaxis and antiretroviral therapy, and have shown bioequivalence in a pharmacokinetic study of co-encapsulated tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (Browne et al., 2024; Chai et al., 2021).

Ingestible sensors have proven effective in improving medication adherence, particularly in the case of TB. A study in India on the use of a digital pill system (DPS) for TB treatment adherence found that 86% of participants accepted the DPS for monitoring adherence. Despite being unfamiliar with the technology, participants viewed it as innovative and beneficial, especially for patients with previous adherence issues or multidrug-resistant TB (Vaz et al., 2022). Furthermore, a randomized controlled trial (RCT) conducted in the USA with advanced-phase TB patients showed a 99.3% accuracy in treatment completion (Ridho et al., 2021). These findings highlight the effectiveness of ingestible sensors in enhancing TB treatment adherence and ensuring accurate tracking of patient progress.

Ingestible sensors have been used not only in the management of TB but also in the treatment of schizophrenia, helping clinicians distinguish between relapses caused by nonadherence and those resulting from a medication's lack of efficacy (Richey et al., 2022). By tracking real-time medication ingestion, these sensors enable more accurate treatment adjustments, ensuring patients receive the appropriate care based on their adherence and the effectiveness of the medication. Moreover, ingestible sensors are proven to be cost-effective. These systems facilitate communication between patients and healthcare providers, leading to direct cost savings. These systems improve adherence, reduce waste, and lower healthcare expenses by influencing market dynamics, demand, and pricing. Healthier patients lead to lower premiums and lower personal healthcare costs (Litvinova et al., 2023).

3.5.3. Safety of ingestible sensor

A bibliometric review of the scientific literature found that the number of publications on digital pills has significantly increased over the last ten years, indicating the growing importance of this topic of study. The study investigated the efficacy and safety of digital tablets in the treatment of significant mental illnesses, TB therapy, diabetes, cardiovascular diseases, and AIDS, emphasizing their potential and safety in a variety of therapies and usage monitoring (Litvinova et al., 2022).

Ingestible sensors are widely regarded as safe, with rare cases of capsule retention in healthy individuals and a low retention rate of 0.33% observed in 6,000 trials. However, patients with digestive complications or prior surgeries may face a higher risk of bowel obstruction. Capsules measuring less than 11 mm in diameter and 28 mm in length are deemed 100% safe, though individuals with pacemakers should avoid them due to potential interference (Manjual, 2024). Additionally, the electronic components embedded in digital pills, including ingestible sensors, have demonstrated stability for over 12 months under standard storage conditions, making them suitable for long-term clinical and research applications without a heightened risk of malfunction (Chai, 2021).

While the electronic stability of ingestible sensors has been shown to be robust, concerns about potential adverse effects related to the sensor's ingestion must also be considered. Ingestible sensors have been shown to be well-tolerated, with a 99.3% accuracy rate in ensuring medication adherence (Ridho et al., 2021). However, concerns about potential adverse effects related to sensor ingestion must be considered. In a study by Ridho et al. (2021), side effects such as mild rashes and itching were reported in 10% of participants, but these were generally minor and resolved quickly, indicating that adverse effects are rare and not severe. Other potential side effects may include gastrointestinal discomfort, nausea, obstruction, and rare allergic reactions. Despite these drawbacks, ingestible sensors hold transformative potential in healthcare, offering significant benefits for patient monitoring and treatment (Manjula et al., 2024).

The safety of ingestible sensors involves not only health aspects but also the protection of personal data collected during their use. Digital pills (DP) raise ethical concerns about data security and privacy, particularly in clinical practice where privacy protection may require more than just secure storage. Patients may feel pressured to use DP if insurers or employers require it, and DP systems may collect lifestyle information, potentially exposing personal behaviors (de Miguel Beriain, 2020). Many studies emphasize that patients should have control over their data, allowing them to choose whether or not to share it with others; nonetheless, societal benefits such as personalized treatment frequently rely on data sharing (Martani, 2020).

3.5.4. FDA approved ingestible sensors for medical treatment and patient care

Ingestible sensors are small electronic devices that can be ingested and integrated into oral medications, such as tablets or capsules. This technology is designed to monitor medication adherence in real time, providing precise tracking of patients' medication routines. By using ingestible sensors, healthcare providers can collect data on patient compliance, which helps enhance treatment effectiveness and ensures that patients follow their prescribed therapy correctly (Goodman et al., 2022). The use of ingestible sensors, or digital pills, has significantly increased in the pharmaceutical industry. Research has demonstrated that this technology can improve treatment outcomes, support therapy progress, and boost patient compliance. Ingestible sensors enable more efficient monitoring of medication intake, ensuring that patients adhere to their prescribed treatments. By incorporating digital technology into medicine, digital pills have a positive impact on health management, particularly in addressing non-compliance, which is a common barrier to successful therapy (Litvinova et al., 2022).

The innovation of ingestible sensors has become a significant breakthrough in monitoring patient compliance during treatment, particularly for diseases like TB. This technology enables real-time tracking of medication intake, ensuring that patients adhere to their prescribed therapy. However, it is essential to conduct trials and assess patient acceptance of this technology to ensure its successful integration and maximize its benefits. The use of ingestible sensors is expected to enhance patient compliance and improve treatment outcomes (Vaz et al., 2022).

With advancements in this technology over recent decades, ingestible sensors present a promising solution for TB management. They offer an effective means of monitoring patient adherence, enabling healthcare providers to ensure proper therapy administration, ultimately leading to better treatment outcomes. This innovation is seen as a major advancement in disease management, contributing to the control of infectious diseases like TB while also improving treatment effectiveness and patient compliance (Litvinova et al., 2023).

In 2012, the U.S. Food and Drug Administration (FDA) approved the first digital medication designed to track consumption. This ingestible sensor technology was applied to aripiprazole, a tablet used to treat schizophrenia, acute manic episodes, and bipolar disorder. Additionally, aripiprazole is prescribed for various other psychiatric conditions, such as adult depression. The ingestible sensor is integrated into the tablet in the form of a small chip, which can be monitored by an external device once the patient consumes it.

The FDA actively supports the development of new technologies in prescription medications, collaborating with pharmaceutical companies to explore how these innovations can benefit both patients and healthcare providers. These technologies are designed to monitor patient adherence to medications, which is essential for ensuring the effectiveness of treatment and preventing non-adherence. One of the FDA's main objectives with ingestible sensor technology is to enhance patient compliance with prescribed medication regimens. High adherence is crucial for successful treatment, reducing the chances of therapy failure, and minimizing the risk of complications, making this technology a key advancement in medication management.

Ingestible sensors also hold significant potential in the management of TB, an infectious disease that requires prolonged treatment. Adherence to TB therapy is often a major challenge, as non-compliance can lead to drug resistance and treatment failure. With ingestible sensors, medication intake can be monitored in real-time, ensuring that patients are following the prescribed regimen. This technology enables healthcare providers to track whether patients are taking their medications as scheduled, which is crucial for the success of TB treatment. This innovation can enhance patient adherence, reduce the spread of the disease, and facilitate more effective TB control.

3.6. Ingestible sensor technology with intervention involving family in monitoring the medication taking of Tuberculosis patients

TB is an infectious disease caused by the bacterium Mycobacterium TB (M.tb). This bacterium is notably resistant to eradication due to its ability to enter a dormant state, ceasing replication after invading the host's body. This dormancy renders M.tb phenotypically resistant to bactericidal antibiotics. Consequently, long-term treatment lasting at least six months is required to eradicate the bacteria by targeting them during periodic exits from their dormant state (Dartois & Rubin, 2022).

The prolonged treatment, the use of multiple drugs, and the social discrimination faced by TB patients contribute to high rates of non-compliance or treatment discontinuation. To address this issue, the World Health Organization (WHO) has recommended the Directly Observed Therapy (DOT) standard of care since 1990. DOT involves drug supervisors (PMOs) who may come from institutions such as health centers or the patient's community, including family members (Sazali et al., 2022). However, DOT is often perceived as inconvenient by health services due to challenges related to distance, time, and cost. A study by Yin et al. (2018) showed that well-trained family members as PMOs could achieve better DOT outcomes compared to healthcare workers. Conversely, other studies revealed that family-based DOT did not outperform healthcare-based DOT, as family members often struggled to understand therapeutic interventions. Nonetheless, psychosocial interventions by family members showed positive impacts on treatment outcomes (Chen et al., 2020).

Although PMOs may observe patients taking their medication, they cannot ensure that the medication is swallowed and not hidden in the mouth. Adherence to medication is crucial not only for TB but also for other chronic conditions, such as mental health disorders. For instance, the pharmaceutical company Otsuka developed an atypical antipsychotic aripiprazole tablet embedded with an ingestible Proteus sensor, integrated via a skin patch sensor into a medical software application, to monitor real-time medication adherence in adults with schizophrenia, bipolar I disorder, and major depressive disorder. This formulation, approved by the U.S. Food and Drug Administration (FDA), has demonstrated efficacy and safety in clinical use (Litvinova et al., 2023).

While this formulation has shown significant therapeutic outcomes, the lack of patient environment involvement, such as family participation, remains an uncontrolled factor for psychosocial interventions, which are vital for the success of chronic disease treatment. Adapting the research concept developed by Otsuka to TB management, integrating therapeutic monitoring technology with family involvement could significantly enhance treatment outcomes for chronic TB infections. Such a combination may prevent active transmission, reduce treatment failure, and curb the development of drug-resistant TB.

3.7. Clinical implication

The use of ingestible sensors in TB treatment monitoring has a significant clinical impact by improving patient adherence through real-time monitoring. This technology allows healthcare professionals to detect non-adherence early, allowing interventions to be initiated before the risk of drug resistance or therapy failure occurs. With the resulting data, treatment approaches can be personalized to meet the specific needs of patients, creating a more effective and outcome-oriented care experience. In addition, this technology reduces the burden of traditional methods such as Drug Monitors (DOMs), allowing caregivers to focus more on emotional support and education.

The higher levels of adherence resulting from this technology directly improve TB treatment outcomes, which in turn can reduce drug resistance rates. Drug resistance to TB is a major challenge worldwide, and reducing this rate would have a significant impact on disease control. Objective data from the sensors also provides important insights for more informed clinical decision-making, such as adjusting doses or treatment schedules based on patient behavior. In addition, this data can support evidence-based health policies, strengthening national strategies to address the TB epidemic.

However, the implementation of ingestible sensors requires consideration of the cost and availability of this technology in resource-limited settings. Patient data privacy is a major concern, given that real-time data collection poses a potential risk of privacy breaches. Therefore, strict regulations and adequate security systems are needed to protect patient data. In addition, health infrastructure, including reliable internet networks, must be in place to support the effective implementation of this technology.

Despite the challenges, the use of *ingestible sensors* in TB treatment opens up great opportunities for innovation in chronic disease management. When combined with family-based interventions to support psychosocial aspects, this technology can lead to improved treatment outcomes. This integrated approach not only addresses biological and clinical challenges but also supports holistic improvement of patients' quality of life. With government support and cross-sector collaboration, this technology has the potential to be a sustainable solution to combat TB globally.

4. Conclusions

Ingestible sensors can eliminate the need for physical space and time in monitoring drug intake. This system can also confirm that patients have actually swallowed the medication, addressing a limitation of the previous DOT method, which cannot ensure that patients do not hide the drug in their mouths. Ingestible sensors, combined with psychosocial interventions through family involvement, are believed to yield better outcomes than therapeutic interventions alone. Implementing therapeutic interventions through drug intake monitoring and psychosocial support via family involvement can enhance the success of TB treatment while reducing the risks of active transmission, relapse, treatment failure, and drug-resistant TB.

A key challenge for the future is ensuring equitable development and economic support across all regions to facilitate the implementation of this system, which primarily relies on an adequate internet network. Therefore, cooperation from all levels of society, especially the government, is essential to realizing the implementation of this system and advancing toward a global movement to eliminate TB.

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Author Contribution
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