



Advances And Challenges In Tuberculosis Diagnosis And Treatment: A Comparative Review Of Traditional And Innovative Approaches

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Abstract:

Tuberculosis (TB) remains a critical global health issue, causing approximately 10 million new cases and 1.5 million deaths annually. Despite the availability of treatment, TB control faces persistent challenges, especially in resource-limited settings. This review examines the nature of TB, including its types, symptoms, and the increasing threat posed by multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). It compares traditional diagnostic methods—such as smear microscopy, culture-based tests, the tuberculin skin test, and chest X-rays—with innovative diagnostic tools like GeneXpert MTB/RIF. The review also explores factors affecting treatment adherence, including socioeconomic, psychological, and systemic barriers, particularly in cases of latent TB. Furthermore, it highlights emerging digital health solutions aimed at improving adherence and monitoring treatment. By evaluating the effectiveness, feasibility, and scalability of both conventional and modern strategies, this article offers insights for policymakers and healthcare providers to enhance TB control, diagnosis, and treatment outcomes globally.

Index Terms - Tuberculosis, digital Technology, TB, MTB.

I. INTRODUCTION

Tuberculosis (TB) is a chronic bacterial infection caused by *Mycobacterium tuberculosis* (MTB) primarily affecting the lungs. Still, it can also affect other body parts, such as the kidneys, spine, and brain [1]. TB is an infectious disease spread through the air when an infected person coughs, sneezes, or talks, and is characterized by its chronic nature, taking months or years to develop. There are four types of TB: pulmonary TB, which affects the lungs; extrapulmonary TB, which affects other parts of the body; latent TB, which is present but not active or contagious; and active TB, which is active and contagious [2]. Symptoms of TB include persistent coughing, chest pain, coughing up blood, fatigue, weight loss, night sweats, and chills. Extrapulmonary TB, affects nearly 15 and 20% of TB patients, especially HIV-positive individuals [3].

Tuberculosis (TB) remains a major global health concern, with approximately 10 million new cases and 1.5 million fatalities annually. Despite significant advancements in medical technology and treatment regimens, TB diagnosis and management continue to pose substantial challenges, particularly in resource-constrained settings [4]. Accurate diagnosis and effective treatment adherence are crucial for controlling the spread of TB and improving treatment outcomes. Treatment for active drug-susceptible TB usually takes at least 6 months, while latent tuberculosis infection (LTBI) can be between 6 and 9 months. The duration of treatment can be longer if the pathogen is resistant to either the first- or second-line of anti-TB medication [5].

Delayed or inaccurate diagnosis can lead to increased morbidity, mortality, and transmission of the disease. Similarly, poor treatment adherence can result in treatment failure, drug resistance, and increased risk of transmission [6]. Numerous factors affect medication adherence, such as poor communication between patient and health care provider, socioeconomic status, health care system factors, patients' mental condition, therapy features, and other patient factors. Moreover, a high risk of nonadherence to the medication has been reported in patients with LTBI because they do not feel any signs or symptoms of the disease but do experience the side effects of the medication [7].

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) caused by *Mycobacterium tuberculosis* bacteria that are resistant to at least two of the most potent anti-TB drugs: **Isoniazid** and **Rifampicin**. This type of resistance complicates treatment, prolonging recovery and leading to worse health outcomes for patients. The rise of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) has further complicated treatment efforts, underscoring the need for innovative solutions [8].

Traditional methods for diagnosing tuberculosis (TB) include acid-fast bacilli (AFB) smear microscopy, culture-based tests, the tuberculin skin test (TST), and chest X-rays. AFB smear microscopy involves staining and examining sputum samples under a microscope to detect TB bacteria, but it has low sensitivity, especially in cases with low bacterial loads [9]. Culture tests are considered the gold standard, as they can identify *M. tuberculosis* and assess drug resistance, though they take several weeks to produce results. The TST detects immune response to TB exposure but cannot distinguish between latent and active TB and may give false positives or negatives. Chest X-rays help identify lung abnormalities associated with TB but cannot confirm the infection or its drug resistance. While these methods have been fundamental in diagnosing TB, they have limitations in sensitivity, speed, and the ability to detect drug-resistant strains like MDR-TB [10,11].

In recent years, innovative methods have emerged to address these challenges. Molecular diagnostics, such as GeneXpert MTB/RIF, offer improved accuracy and rapid turnaround times. Digital health technologies, including mobile health (mHealth) applications and electronic adherence monitoring systems, have shown promise in enhancing medication adherence and treatment outcomes [12].

This comparative analysis aims to evaluate the effectiveness, feasibility, and scalability of traditional and innovative methods for diagnosing TB and enhancing medication adherence [13]. By examining the strengths and limitations of each approach, this analysis seeks to inform evidence-based decisions and policy recommendations for improving TB diagnosis and treatment outcomes globally [14].

Traditional Methods of Diagnosis

Sputum Smear Microscopy

Sputum smear microscopy (SSM) is one of the techniques widely used to diagnose active PTB. It identifies acid-fast bacilli through acid-fast staining's such as Ziehl–Neelsen (hot stain) or Kinyoun (cold stain), whose principle involves the binding of carbon fuchsin to the mycobacterial mycolic acids [15].

Ziehl–Neelsen staining is cost-effective (mean cost USD 13.31) but may underestimate bacterial burden, as well as presenting variable sensitivity (32% to 89%). Furthermore, this technique cannot differentiate between dead and live bacteria, drug-susceptible from drug-resistant strains, nor distinguish *M. tuberculosis* from other mycobacteria, exhibiting compromised sensitivity whenever the bacterial load is less than 10,000 bacilli/mL sputum sample [16]. A study performed by Chopra et al. showed that Kinyoun's method presented higher sensitivity (98.37%) compared to Ziehl–Neelsen staining (89.25%), indicating it is more effective at detecting tubercle bacilli [17].

Fluorescence microscopy can save manpower and improve work efficiency, as well as increase the sensitivity of smear microscopy. The possibility of false-positive results is a potential shortcoming of fluorescence microscopy, because of non-specific fluorochrome dye incorporation. The instability of fluorescent staining has been reported. Unlike conventional microscopy using conventional artificial light, fluorescence microscopy uses an intense light source, such as a halogen or high-pressure mercury vapor lamp, which is expensive and vulnerable [18]. However, in comparison to intense light sources, light-emitting diodes (LEDs) are more robust, sustainable, and have a longer-lasting battery life expectancy, and these qualities make LED microscopy feasible for use in resource-limited settings. Accordingly, the WHO recommends that conventional fluorescence microscopy can be replaced by LED microscopy [19].

Fluorescein diacetate (FDA) is a new stain solution where only living cells actively convert the nonfluorescent FDA into the green fluorescent compound following enzymatic activity. FDA staining can be used to detect the viable *Mtb* and simply predict the quantitative culture results within 1 h, indicating whether patients are responding to TB therapy [20]. "TBDx" is an innovative smear microscopy system that automatically loads slides onto a microscope, focuses and digitally captures images, and then classifies smears as positive or negative using computerized algorithms. Despite showing potential for detection of *Mtb*, these new microscopy methods still need more validation of their performance in clinical practice [21].

Notably, SSM should be combined with other diagnostic tools to enhance the efficacy and reliability of TB diagnosis. Despite the diffused employment of molecular approaches, researchers underscore that SSM remains fundamental as the primary diagnostic technique for TB globally, with high-burden countries conducting millions of smears annually [22].

Culture Methods

Solid and Liquid Culture

Culture is still the WHO-recommended gold standard for the diagnosis of TB, as *Mtb* isolation is not only important for disease diagnosis but also permits the detection of drug resistance. Traditional *Mtb* culture can be performed on either a solid (e.g., Lowenstein–Jensen) or liquid (e.g., Middlebrook 7H9) medium. Notably,

solid culture is less expensive than liquid culture and less prone to contamination by other bacteria or fungi, but liquid culture is faster, more sensitive, and convenient (growth is detected automatically) [18].

The 'gold-standard' for positive diagnosis of TB is the use of traditional plate culture, typically conducted in a high containment laboratory, due to the inherent risk associated with working with Mtb. The culturing of Mtb raises several issues, mainly relating to the growth rate of Mtb, which is substantially slower than other pathogenic organisms, most probably due to a selective pressure at which faster growing *Mycobacterium* spp. induces a greater immune response. It can often take more than four weeks for Mtb to produce colonies using traditional Lowenstein–Jensen medium (LJ) (solid culture). An advantage of plate culture is that drug sensitivity testing can take place concurrently, enabling clinicians to guide antimicrobial therapy more effectively [23].

A technical detail that should be mentioned is sample decontamination. Samples (such as sputum) that are contaminated with normal flora must undergo decontamination before culture. The laboratory can use a routine decontamination reagent such as NaOH together with N-acetyl-L-cysteine (NALC), which kills rapidly growing bacteria and fungi but has a limited effect on Mtb growth. The laboratory should determine the optimal concentration of decontamination reagent, to avoid over-decontamination (which reduces the yield of Mtb) and under-decontamination (which leads to failed cultures, because of high rates of bacterial or fungal growth) [24].

Rapid Identification from Positive Cultures

Rapid identification assays capable of distinguishing between Mtb complex and NTM after positive cultures are the basis for initiating early anti-TB therapy. Traditional biochemical assays are slow and have a long turnaround time (2–3 weeks). Mtb protein 64 (MPT-64) is one of the Mtb-specific antigens secreted during bacterial growth. Immunochromatographic (ICT) assays are based on the principle of a double-sandwich enzyme-linked immunosorbent assay, which detects MPT-64 antigen [25]. A recent review reported a high sensitivity (range, 98.1 to 98.6%) and high specificity (range, 99.2 to 100%) of ICT assays for rapid identification of Mtb complex. In addition, ICT assays are rapid, simple, and without the need of additional special equipment. Therefore, the WHO recommends using ICT assays for rapid identification of Mtb complex from positive cultures [26].

Phenotypic Tests for DST

Testing on solid agar using the proportion method is still regarded as the reference standard method for DST of Mtb, which is performed by counting the number of MTB colonies that grow on agar with or without antibiotics. The absolute concentration method is based on the comparison of growth intensity in the presence of cutoff concentrations and on drug-free controls [27]. Commercial automated liquid culture systems (e.g., the mycobacteria growth indicator tube system) use a modification of the proportion method and offer reliable results for two important first-line drugs (isoniazid (INH) and Rifampin (RIF)), while the testing for resistance to second-line drugs is less reliable and reproducible. Other methods have also been reported, such as microscopic-observation drug susceptibility assays (using inverted microscope to observe the characteristic spiral or comma-shaped microcolonies of growing mycobacteria in liquid culture), thin-layer agar (identification of isolates based on the characteristic morphology of mycobacteria in solid culture), and

colorimetric redox indicator (observation by a change in the color of the culture medium containing anti-TB drugs) [28]. The current data suggest that these assays could be used for a rapid and accurate DST, in settings where WHO-endorsed assays are not available. Generally, the sensitivity of Mtb culture is higher than smear, and Mtb culture is still one of the most important methods for the diagnosis of TB. However, false-negative results of Mtb culture are inevitable in real clinical practice, and using the method for diagnosing TB in paucibacillary samples is still challenging, leading to its inability to rule out TB. Another limitation is that the growth of Mtb in conventional mediums takes from 4 to 8 weeks, with an additional 4 weeks for DST using the conventional proportion method. In addition, Mtb culture requires biosafety facilities and specially trained laboratory technicians to perform the experiment. Hence, Mtb culture is recommended to be performed at national reference or central laboratories, in some areas [29].

Immunological Diagnosis

Antibody Detection

Serologic tests rely on antibody recognition of Mtb antigens by the humoral immune response. Owing to the poor diagnostic sensitivity and specificity, the WHO does not recommend any commercial serologic assays for the diagnosis of TB, in case of misdiagnosis and resource waste [28;29].

Antigen Detection

The presence of circulating Mtb antigens can be detected from clinical specimens such as sputum, serum, and urine, based on the principle of sandwich enzyme-linked immunosorbent assay. Lipoarabinomannan (LAM) is a specific component of the cell envelope of Mtb and can be a potential biomarker for TB diagnosis. FujiLAM is a urine lateral flow LAM test. The sensitivity and specificity of FujiLAM are 70% and 93%, respectively, in adult TB, while the sensitivity and specificity in children with TB are 51% and 87% [30].

Tuberculin Skin Testing (TST)

TST is a classical method based on detection of type IV hypersensitivity using purified protein derivative (PPD) of tuberculin. Mtb-infected patients can produce sensitized T lymphocytes with the ability to recognize Mtb antigens. When the sensitized T lymphocytes are stimulated by Mtb antigens again, a variety of soluble lymphokines are released to increase the vascular permeability, local redness, swelling, and induration. The average diameter of induration is measured after 72 h of PPD injection as the results of TST. An average diameter of induration <5 mm or no response is considered as negative; ≥ 5 mm is considered as positive [30;31].

The following factors can influence TST results:

Bacillus Calmette-Guerin (BCG) vaccination: Since BCG and PPD share antigenic components, the specificity of TST can be affected by BCG vaccination. The effect of BCG vaccination on TST in infancy is minimal, especially ≥ 10 years after vaccination. BCG vaccination strategy (whether or not to multiply) also affects TST results, and the effect of BCG booster immunization on TST is more pronounced compared with the current BCG one-time vaccination [32].

NTM infection: NTM is not a clinically important cause of false-positive TST, except in populations with a high prevalence of NTM infection and a very low prevalence of TB infection [33].

The host's immune status: Since TST detection is based on Mtb-specific immune response, the host's immune status will affect TST accuracy. Therefore, the sensitivity of TST for diagnosis of TB is reduced in patients with immunocompromised conditions. A systematic review of the investigation of Mtb infection in immunocompromised populations showed that TST sensitivity decreased to 31% in haemodialysis patients. Another study showed that immunosuppressed organ transplant recipients will likely develop anergy to the tuberculin antigen, which leads to false-negative TST results [34].

T-SPOT

T-SPOT assay, based on the enzyme-linked immune spot (ELISPOT) method, detects the number of IFN- γ -producing cells after Mtb-specific antigen stimulation. Currently, the T-SPOT assay is widely used to diagnose Mtb infection. T-SPOT has proven useful, not only in detecting Mtb infection in children and HIV patients, but also in the assessment of risk for TB development in chronic inflammatory diseases, before anti-TNF treatment and screening for latent tuberculosis infection (LTBI) in immigrant groups, healthcare workers, and college students. T-SPOT has also been reported to be a useful adjunct test for diagnosing extrapulmonary TB [34;35].

Radiographic Techniques

Chest radiography/chest X-ray (CXR) is very useful for TB diagnosis, particularly in resource-limited settings, showing high sensitivity in detecting PTB but limited specificity. According to the World Health Organization (WHO), this technique exhibits a sensitivity ranging from 87% to 98% and is considered a valuable tool for screening PTB [36].

Performance of frontal anteroposterior and lateral chest X-rays is indicated whenever TB is suspected, be it pulmonary or extrapulmonary. Chest X-rays are also indicated in children with a diagnosis of TBI (positive tuberculin skin test or IGRA) and for evaluation of at-risk patients (immunosuppressed patients of any age and children aged less than 2–5 years) exposed to TB [37].

Although this continues to be the recommended imaging modality for the initial assessment of TB, it is nonspecific, does not always detect characteristic features, and shows considerable interrater variability in its interpretation. Computer-aided detection software is already being used for the interpretation of chest X-rays in the assessment of TB in adults, and several such systems are available [38].

New Diagnostic Methods

A. Molecular Diagnostic Techniques

Xpert MTB/RIF

GeneXpert MTB/RIF is the most widely used detection method in molecular diagnostics. It is a semi-nested real-time fluorescent PCR for the detection of *M. tuberculosis* and Rifampin resistance simultaneously. The Xpert MTB/RIF Ultra developed based on Xpert MTB/RIF increases two different multi-copy amplification targets and a larger DNA reaction chamber [39]. This technology directly detects MTBC DNA in sputum or concentrated sputum deposits as well as Rifampin resistance, producing results within 2 hours.

In consideration of high demands for professional testing personnel and supporting infrastructure, the primary medical institutions have difficulties to meet the above requirements for Xpert MTB/RIF and ensure the quality of test results [40].

Loop-Mediated Isothermal Amplification

Loop-mediated isothermal amplification is a type of Nucleic Acid Amplification Test that employs DNA polymerase and a set of specially designed primers to detect the presence of pathogenic DNA from a patient sample. The SS-LAMP is specially designed with a set of six specific primers to identify eight different regions on the MTBC-specific repeat insertion sequence 6,110 (IS6110), which is qualified to directly detect the DNA of MTBC from liquefied sputum samples [41].

A validation study of the method was performed using 157 liquefied sputum specimens from Moroccan suspected TB patients. SS-LAMP analysis is faster, with a specificity of 99.14% and a sensitivity of 82.93% compared with the conventional L-J solid culture method. LAMP method is suitable for areas where medical resources are relatively scarce [42].

Digital PCR

Digital PCR (dPCR) is a new type of nucleic acid quantification technology that requires very small amounts of target molecules, and it performs the absolute quantification without the need for a standard curve. Therefore, dPCR is precise and sensitive, and most importantly, it detects single copies of DNA. The dPCR samples can be sputum, blood, formalin fixed paraffin embedded tissue, and exhaled breath [43].

The drug sensitivity testing can also be performed by this method. IS6110 is a common target for dPCR amplification, but when combined with IS1081 and IS6110, the dPCR sensitivity is higher than IS6110 qPCR, thus improving the diagnosis of smear-negative TB [44].

This method has been demonstrated as useful for studying in the case of lung, extrapulmonary, latent TB infection, and active TB, though more prone to error in the hands of inexperienced users [44].

B. Serological Tests

Next-generation sequencing techniques

Another approach to the diagnosis and surveillance of Mtb is to utilize next-generation sequencing (NGS) technology to sequence Mtb genomes allowing diagnosis, screening of these genomes for resistance-conferring mutations, and determining their relatedness for public health purposes [45]. Drug sensitivity testing (DST) can be achieved via targeted or whole-genome sequencing (WGS) approaches. Targeted NGS approaches, such as the Deeplex-Myc TB assay, are focused on known resistance-conferring loci, whereas WGS is focused on sequencing the entire genome [46].

WGS offers several advantages the foremost being its inherent flexibility and the accuracy of predictions can be improved iteratively due to better models being developed. A genomic epidemiological approach, where Mtb transmission clusters are identified phylogenetically allowing evidence-based interventions to be utilised to control Mtb transmission more effectively on a population-wide scale can only effectively be achieved with WGS [47].

Digital droplet PCR

More recent developments have started utilising some of the newly emerging technologies such as, digital droplet PCR (ddPCR). ddPCR is a more recent innovation which partitions the amplification reaction seen in PCR; this way, it provides an absolute quantification of gene expression rather than a relative one. Due to this, its sensitivity is higher than qPCR, and this method is capable of detecting single copies of DNA [48].

This technique has already been used to monitor mixed populations of cells to better understand drug-resistance [49]. Whilst ddPCR offers a greater amount of sensitivity than quantitative or qPCR methods and can be used to test for Mtb infection in both sputum and blood samples, and therefore useful in cases of pulmonary, extrapulmonary, LTBI and active TB, though its main drawback is that it can be prohibitively expensive [50;51].

Clustered Regularly Inter Spaced Repeats

Clustered Regularly Inter Spaced Repeats or CRISPR and its combined use with CRISPR-associated nuclease 9, Cas9 (Figure 1) is a technology that is often thought of as a gene-editing technique. Essentially, it has acted as a programmable enzyme that can 'cut' DNA in specific places, though recent discoveries have identified more enzymes that possess collateral activity as well as an ability to target single-stranded DNA, as is the case with Cas12a [52].

Contemporary research has demonstrated that this technique could be used to detect Mtb DNA. This is particularly noteworthy due to its potential to be lyophilized onto a lateral flow stick with Atto molar sensitivity, enabling it to be readily deployed in areas where electricity is seldom available [53].

Mass Spectrometry

Regarding mass spectrometry, Matrix-Assisted Laser Desorption/Ionization Time Of-Flight Mass Spectrometry (MALDI-TOF MS) is revolutionizing clinical microbiology by rapidly and accurately identifying microorganisms in various samples, potentially improving patient outcomes, and reducing hospital stays [54].

Some studies present the use of nucleotide MALDI-TOF-MS and MALDI-TOF-MS as promising rapid tools for detecting drug resistance in M. tuberculosis, as well as the simultaneous detection of MTBC and mutations related to drug resistance, although these techniques cannot identify de novo drug resistance mutations nor detect mutations related to novel resistance mechanisms [55].

Raman spectroscopy

Raman spectroscopy (RS) is another portable analytical tool, which could be readily deployed into rural areas. RS has been utilised in many other applications, such as the diagnosis of cancer and to identify bacterial infections [56].

The technique utilizes the phenomenon of Raman scattering to detect the unique molecular fingerprints of various bacteria when subjected to an excitation with a certain wavelength of light. Preliminary research has demonstrated its ability to detect TB alone (both drug-sensitive and drug-resistant serotypes), however no research exists as to its efficacy outside of a monoculture sample (a critical objective if such a device were to make it to market) or alternative samples to blood [57;58].

The successful development of an RS based method would enable clinicians to rapidly screen through a vast number of patients due to Raman's ability to scan a sample within a matter of minutes, as opposed to many hours other molecular methods use [59].

AI processing

One of the main uses of AI in TB is using machine learning to automate the diagnosis of disease. The common strategy is to establish expert systems using a machine learning method based on the clinical, radiological,

and laboratory data of TB patients. Interesting, machine learning has been reported to aid clinicians in diagnosing pulmonary TB or predicting drug-resistant TB. For instance, Lopes et al. presented three proposals for the application of pre-trained convolutional neural networks as image feature extraction to detect TB disease [60;61;62].

Medication Adherence in Tuberculosis Treatment

Importance of Adherence

According to Delamater, “adherence” is the active, collaborative, and voluntary involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result. It means that patients and healthcare professionals should mutually agree on predefined goals regarding treatment and medical regimens. If these goals are not followed, miscommunication between healthcare professionals and patients compromises patient care and potential complications associated with the disease may occur. Failure to adhere to the prescribed medication is linked with higher relapsing rates, higher readmission rates, poor clinical outcomes, increased morbidity and mortality, and increased healthcare costs.

According to WHO’s recommendation, adherence factors are categorized into five dimensions, those associated with the healthcare team, socioeconomics, therapy, patient and illness. Non-adherence to medication can also be regarded as either intentional or unintentional.

Intentional non-adherence mentions those conditions in which patients intentionally choose to either stop or reduce administering their prescribed medications. It is completely depending on the motivation level of patients.

Unintentional non-adherence is associated with patients’ lack of cognitive ability and capacity, that compromises the ability of the patients to adhere to the treatment regimen, e.g., cognitive impairment and forgetfulness can impact the patients’ adherence. The intentional and unintentional cases are not mutually exclusive concepts, as poorly or less motivated patients, in most of the cases forget to take their medicines.

Consequences of non-adherence

Tuberculosis (TB) remains one of the most pressing public health issues globally, particularly in countries with high incidence rates such as Indonesia. The disease poses significant challenges due to its complex nature and the increasing emergence of drug-resistant tuberculosis (DRTB). DR-TB, particularly multidrug-resistant TB (MDR-TB), threatens to undermine global TB control efforts, making it a critical area of concern for public health authorities.

The World Health Organization (WHO) has highlighted that inadequate or non-compliant treatment regimens are the primary drivers of bacterial resistance to anti-tuberculosis drugs (OAT), leading to the proliferation of DR-TB cases. Globally, medication non-adherence has been recognized as a significant factor contributing to the development of drug resistance in TB patients.

Nonadherence to TB treatment, whether intentional or unintentional, disrupts the efficacy of the treatment regimen, allowing the bacteria to survive and develop resistance. This issue is not only prevalent in low-resource settings but also in developed countries, where various socioeconomic factors impact patients’ adherence to prescribed medication protocols.

Despite the extensive research on TB treatment adherence and its impact on health outcomes, there remains a significant gap in understanding the specific factors contributing to non-adherence in high-burden areas like Indonesia, where the incidence of DR-TB is particularly alarming. While previous studies have established a general link between non-adherence and the development of DR-TB, there is a lack of comprehensive research that integrates socio-economic, cultural, and psychological factors influencing patient behavior in this context. Moreover, existing studies have often focused on broad geographic regions, neglecting localized studies that could provide more nuanced insights into the specific challenges faced by different communities.

Public health implications

Poor or inadequate adherence to prescribed regimens cause negative effects on health and economic status of an individual. Various studies have demonstrated that up to 50% of patients do not adhere to the prescribed medications which will ultimately result in relapse and rehospitalization, enhanced drug wastage through excessive dosage, enhanced resistance to drugs, and make it more challenging for the physicians to assess effectiveness of the treatment. Although the World Health Organization (WHO) believes that enhancing adherence rates can deliver more health benefits than refining particular treatments.

Traditional Approaches to Improving Adherence

Accurately measuring and monitoring patient medication adherence is critical in clinical practice and research settings but continues to be a challenging task globally.

Various methods are used to measure medication adherence, such as patient self-reports, pill counts, pharmacy refill records, drug metabolites or biomarker testing, and directly observed therapy (DOT). However, none of these methods have been accepted as a standard measure of medication adherence across a variety of settings. More recently, sensor technologies have been increasingly used to track the medication-taking behaviors of patients. For example, the Medication Event Monitoring System (MEMS) can record every time the patient opens the pill bottle via a sensor embedded in the pill cap. Such technologies provide a unique opportunity to measure and monitor patient medication adherence over time.

There is limited consensus on how to determine or select the appropriate medication adherence monitoring technology for use, which may be due to the lack of appropriate technology assessment criteria in this field. The advantages and limitations of the commonly used methods for measuring medication adherence have been described in the literature. For example, DOT allows for direct observation of patient medication-taking actions, but it is expensive to sustain and produces a constrictive time strain on both health care providers (HCPs) and patients' daily schedules.

As a common way to measure medication adherence, patient self-reporting respects patient autonomy but carries the potential risk of patient overestimation or underestimation of their adherence abilities. Medication adherence monitoring technologies with various types and features are being continuously developed and upgraded. Some newly developed technologies may possess unique features that are unfamiliar to users.

Innovative Strategies for Enhancing Adherence

Digital Health Interventions

Integrating electronic health (eHealth) into medication prescription, dispensing, and administration processes is a promising step in the direction of achieving better medication safety, treatment, and health outcomes. Health technology that supports patients' medication management can be integrated into different media including mobile health (mHealth), telehealth, SMS, and wearable devices.

Offering a range of functionalities such as remote consultation and monitoring essential health indicators, eHealth plays essential roles in informing, educating, connecting, monitoring, and motivating patients. eHealth might provide an opportunity to offer accessible, interactive, timely, and feasible medication adherence interventions that require minimal effort from healthcare providers whose time and resources are limited. eHealth or telemedicine—these words are used interchangeably—is defined as the use of information and communication technology in health care.

These technologies can facilitate tailored and interactive solutions such as targeted education, consistent support, and skill acquisition. Thus, the multifaceted and versatile medication-taking behaviour can well be targeted by eHealth interventions.

A variety of methods have been evaluated to improve adherence, including financial incentives to patients, labour-intensive intervention, and information technologies regarding health (such as smart drug packaging, automated dispensers, and feedback systems). Smart packaging technology possesses many forms, with some integrated features such as condition monitoring, event recording, feedback mechanisms, reminder systems, status displays, and anti-counterfeiting technology.

These features are integrated with intervention programs that have been proven to be the most consistent in improving adherence. Besides these merits, smart packaging technology possesses limitations like ease of use, dosage flexibility, and cost. Examples of these technologies include Med-ic smart blister packaging and eCap™ pill bottles.

Electronic pillboxes and reminders

Electronic pill boxes or bags record a date-and-time stamp whenever they are opened. However, unlike electronic pill bottles, these technologies can often store multiple types or strengths of medication in various compartments within the device. The size and storage capacity vary among the different types of available electronic pill boxes or bags. Most of the identified electronic pill boxes or bags possessed the ability to transmit patient medication adherence data in real time via existing cellular networks, wireless Bluetooth, or general packet radio service.

One device required manual uploading of patient adherence data during clinic visits. Although the capability of these devices to store multiple medications makes them better suited for complex multidrug regimens, this advantage is dependent on the device, as they can vary drastically in size and pill storage capacity.

Smart blister and smart drawer

Smart blisters are referred as pharmaceutical packaging that possesses the capability of tracking the action of taking out a pill. Besides this the printed circuitry in the packaging also collects the information regarding the rupturing time, medication category and name, location etc. By utilizing the smart blisters patients can also

get pill reminders on their mobile phones. Additionally, if any type of misconception occurs during the course of medication, both physician and patient can check whether they have taken the prescribed medication at correct time or not. This will minimize the medication error and create a two-way monitoring process that will ultimately help in enhancing the medication adherence of patients.

Mobile apps for tracking and support

According to WHO, mHealth or mobile health is regarded as practices concerning public and medical health that are aided by mobile device such as PDAs, mobile phones, patient monitoring devices, and other wireless devices. mHealth utilizes the mobile phone utility of voice and short messaging service (SMS) along with complex application and services like infrared, Bluetooth, global positioning system, third and fourth generation mobile telecommunications (3 G and 4 G technology). In 2009, WHO conducted a survey considering mHealth in various regions. Results obtained in survey demonstrated that more than 80% of the participating member states confirm the existence of at least one mHealth initiative in country. Among the participating groups, 75% reported the presence of four or more types of mHealth initiatives. There were only 19 countries that did not confirm the existence of mHealth initiative. However, zero reporting of mHealth initiatives does not mean that no mHealth initiatives are being carried out in countries. Local and small mHealth project being carried out by non-government or private organizations that may not be extensively recognized. Additionally, the survey was restricted by the fact that participants could only provide the instance of each mHealth group. Therefore, the frequency of the mHealth initiatives reported demonstrated the scope of mHealth projects in a country but does not depict the detail of project within each category.⁶⁴ Participating African regions reported very less projects regarding mHealth, while in southeast Asian regions reporting was more. According to the World Bank, the low-income participant groups reported very few mHealth initiatives in their regions. However, the results of high-income category were not significantly higher when compared to low-income groups regarding the context of mHealth. Depending on the diverse localization of reported mHealth projects initiatives both economically and geographically, it seems that mHealth is a methodology with global appeal.⁶⁴ The participating countries that reported the mHealth initiatives includes emergencies, emergency toll free services, mobile telemedicine, healthcare telephone helplines and healthcare call centres. These mHealth project initiatives functions on the voice functionality of mobile phone and depicts the major portion of these projects. There were also the projects that involve the applicability of mobile phone in surveillance, decision support systems, health surveys and awareness raising campaigns. The results that were obtained from the present literature were different from the reports that advocate the applicability of mobile phone in disease surveillance and data collection. However, most of the studies were based on perceiving the effectiveness, feasibility and differences between convectional approaches of data collection and surveillance of diseases to mHealth solutions. Therefore, these project initiatives may not be visible to government informants or officials that conduct the survey.⁶⁴ Subsequently, it is important to note that diagnosing a disease with the help of mobile phone requires that integration of more sophisticated technology. Since this would require integration of more specific sensors that could detect the presence of disease by simply opening a program that receives and transmits diseases related data from the central servers and by incorporating the

application of artificial intelligence the diseases can be identified. Such initiatives are expected to increase in near future, however, as artificial intelligence is becoming more advanced day by day. (8).

Intervention Strategies

To describe intervention strategies among effective interactive eHealth interventions we used Lowe's taxonomy as it is specific for adherence interventions with clear examples for each strategy. Although other taxonomies (eg, Abraham and Michie [53], Demonceau et al [54], Kini and Ho [7]) could have been used, they show many conceptual similarities with Lowe's taxonomy. Following Lowe's taxonomy, we provide evidence for interactive adherence interventions aimed at teaching skills such as self-management programs, improving health care quality by coordinating medication adherence care between professionals, and facilitating communication or decision making between patient and health care professional. These results should be interpreted with caution because interventions were multifaceted and combined different strategies. Furthermore, the strategies with the highest level of evidence were also those that were less used. It is not possible to assign success to a single strategy within a multifaceted intervention. Nonetheless, the effective strategies we identified in this review suggest to be good starting points for development or selection of interventions.(9)

Impact of smart technologies on healthcare systems

Advanced technology has collaborated in numerous ways to reveal the probability of pharmacological treatment ultimately. Understanding the various pathways and development of better treatments does not benefit instantly until they are subjected to validate the benefits possible. However, numerous studies have demonstrated that adherence holds the good impact on economic and clinical outcomes as well as on utilization of health services. Cost is important factor in deciding whether patients repurchase the prescribed medications or not. Therefore, factors that aid in lowering the cost of medications will surely help in improving the adherence. For some medicines, modern technology has aided in lowering the price of the drug and also improved its safety. The efforts to promote generic prescribing are important measure in reducing cost. The utilization of internet now offers various generic alternatives of costly drugs. Now patients can obtain more information about their diseases by utilizing the web-services supported by the internet to understand and manage their diseased condition which comprises of decreasing the costs of their prescribed medication, such as anti-cancer medications. Many patients having chronic diseases are provided with different medication regimens that are to be taken with varying schedules, that includes growing number of geriatric patients diagnosed with memory and cognitive problems, various pharmacies have started packing the medications in dosette box or Webster-pak® which employs advanced technology to seal the medicines into blister packs that blocks the mixing up of various medications, clearing the confusion of taking the medications. Technology provided more potential of advanced pill box systems, in which product is linked through wireless connection to a central server that tracks the patient dosage activity.⁶⁵ The dosage activity of the patients can be viewed online by physicians or patient or caregivers and is programmed remotely through wireless connection. It gives the features of complete reminders by employing beeps, text-messages, e-mail, beeps and flashing lights. Also, the system can be programmed to send weekly reports via email. The development of medicine prescribing computer programs that are connected to an online pharmacopeia aids

in identifying side-effects, indications, contra-indications as well as drug interactions will ultimately enhance the accuracy and legibility of prescribed medications. These improvements can be utilized for providing more safe and efficient prescribing practices that can help the patients for which the treatment is prescribed. The growing applications of mobile phones or similar devices that can be carried close proximity with its owners, integrated with SMS utility and automated message sending, has increased the frequency of employing voice calls and SMS for health allied calls. Mobile phones and devices are specifically employed for appointment reminders that ultimately enhance the adherence. Apps for smart phones can also provide services like heart rate monitor, body temperature monitor, electrocardiogram etc. that can be more useful in monitoring the health and prevents any type of misconception regarding health. Interaction of patients with the physicians establishes the platform for whether patients have confidence in the prescribed medication or not. The vitality of confidence and trust for the physician is very critical inpatient adherence. Advanced technology may have positive or negative effect on aspects associated with patient adherence, based on the attitude and behavior of the medical practitioners. The accessibility of online information regarding prescribed medications (due to miscommunication between physician and patient which leads to its verification) can result in lack of desire in administering new medications if the risks behind them are not given. This results in consumption of time during the course of medication. However, the time spent in attending the concerns of patients can build the better relationship between patient and physician, sometimes results in alteration in diagnosis and therefore indirectly enhances the adherence. New technologies can aid health care providers in providing information via distance education for professional development.(8)

Challenges to smart technologies concerned with improving adherence

Till date, European Medicine Agency and U. S. Food and Drug Administration do not implement smart adherence monitoring systems in case of clinical trials. Also, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has changed its ICH-E9 guideline introducing the new term “estimand” which is related to technical requirements for Pharmaceuticals for human use.⁶⁶ Previously, the efficacy of the analysis of the drug was purely based on principle of intention-to treat but the revised guideline speculates a more accurate parameter of treatment effect which defines the dealing parameters in case of non-adhering patients. However, there was no citation of difference between poor adherers, non-initiators and discontinued patients. This ultimately hinders appropriate distinction between a simply non adhering and true ‘pharmacological’ non responder patient.⁶⁷ In the screening of efficacy of drug, it is very important to think on this distinction before concluding that drug is not therapeutic based on black box of real time medication use. Therefore, the need of formal guidelines is required; this would require joint efforts of healthcare professionals and regulators. Indian government has set up primary healthcare centers (PHC) throughout the country to provide affordable and quality healthcare services. However, the connectivity at these PHCs is not satisfactory. Therefore, PHCs are unable to offer real-time healthcare solutions to the patients based in remote areas. The mHealth infrastructure in India must undergo strict and drastic alterations. There is a need to make cost effective and sustainable ecosystem and infrastructure that will facilitate implementation of mHealth across the country. The capital required to develop this infrastructure is a big concern as there are inadequate funds available. Solution for facilitating

enough funds for development of stable healthcare infrastructure is to pool funds and resources from other schemes of government that will ultimately create a robust infrastructure that will ultimately serve various sectors such as healthcare, education, finance etc.(8)

Conclusion

Tuberculosis remains an important cause of death among infectious diseases, with granulomas as the hallmark of its pathophysiology. Since a wide range of the population is estimated to be infected with *M. tuberculosis*, exhibiting no symptoms, the infection can become active upon a series of factors, including the interaction between the pathogen and the host immune system. An important consequence of tuberculosis reactivation is the significant risk of transmitting *M. tuberculosis* to other individuals, which can amplify the spread of the disease within the community. This review addresses the multiple approaches to diagnosing tuberculosis (1), approach in improving medication adherence and treatment outcomes among patients with TB despite the variable intervention effects that were discovered(7), a summary of the current technological features and data capture methods, reports the advantages and limitations of medication adherence monitoring technologies for pill form medications, and proposes a potential technology assessment criteria.(6)

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