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A Literature Review: Effectiveness and Efficacy of Whole Genome Sequencing in predicting *Mycobacterium tuberculosis* Drug Resistance in Indonesia

Nurul Widyawati[1*)], Ronald A Parubak[2], Ida Rizqa Nuraini[3], Henny Tantono[4], Ketut Suhendro[5], Jeremy Sebastian[6], Rina Puspasari Suryana[7], Indra Fauzi Sabban[8], Sri Wahyuni[9]

[1] Bhakti Wiyata Institute of Health Science, [2] Bhakti Wiyata Institute of Health Science, [3] Bhakti Wiyata Institute of Health Science, [4] Bhakti Wiyata Institute of Health Science, [5] Bhakti Wiyata Institute of Health Science, [6] Bhakti Wiyata Institute of Health Science, [7] Bhakti Wiyata Institute of Health Science, [8] Bhakti Wiyata Institute of Health Science, [9] Bhakti Wiyata Institute of Health Science

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*) Corresponding author:
E-mail: nurul.widyawati@iik.ac.id

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Abstract

Purpose: Tuberculosis (TB) remains a considerable public health problem in Indonesia, particularly due to the rising burden of multidrug-resistant tuberculosis (MDR-TB). Rapid and accurate drug resistance detection is crucial to advance treatment outcomes and limit transmission. This objective of this literature review is to evaluate the effectiveness and efficacy of whole genome sequencing (WGS) in predicting *Mycobacterium tuberculosis* drug resistance in Indonesia.

Methods: This literature review was conducted through scientific databases such as PubMed, Scopus, and Science Direct. Keywords included "*Mycobacterium tuberculosis*," "drug resistance," and "whole genome sequencing." Eligible studies were original research articles, clinical guidelines, and meta-analyses published within the last 10 years, written in English or Bahasa Indonesia, and available in full text. Relevant findings were systematically reviewed and synthesized.

Results: The reviewed literature demonstrates that WGS shows high sensitivity and specificity in detecting first-line anti-tuberculosis drug resistance, particularly rifampicin and isoniazid. Compared with conventional phenotypic drug susceptibility testing, WGS offers a significantly shorter diagnostic turnaround time and enables comprehensive identification of resistance-associated genetic mutations. Studies from high- and low-middle-income settings indicate strong concordance between WGS and culture-based methods. However, limitations include high infrastructure requirements, the need for bioinformatics expertise, and reduced predictive accuracy for some second-line drugs.

Conclusion: Whole genome sequencing is an effective and promising tool for predicting drug-resistant TB and has the potential to strengthen TB control strategies in Indonesia. Targeted investment, capacity building, and integration with existing diagnostic systems are required to support its broader implementation and contribution to the WHO End TB Strategy.

Keywords: tuberculosis, whole genome sequencing, drug resistance, *Mycobacterium tuberculosis*, Indonesia

Introduction

The *Mycobacterium tuberculosis* complex (MTBC) pathogens are jointly the leading cause of death by infectious cause globally, accounting for approximately 10 million new cases each year. Notably, an increasing number of these cases exhibit resistance to rifampicin and isoniazid, categorizing them as 'multidrug-resistant TB.' To effectively combat the dissemination and drug resistance of *M. tuberculosis*, a unified global strategy focusing on prevention, diagnosis, treatment, and surveillance is imperative. Recent advancements in public health research initiatives, encompassing contact tracing and phenotypic methods for drug susceptibility testing (DST), have been augmented by molecular approaches. These latter methodologies enable swift diagnostics, comprehensive drug susceptibility profiling, and elucidation of *M. tuberculosis* transmission patterns.[1]

Next-generation sequencing (NGS) arose as a significant technological advancement in the management and control of TB. Whole-genome sequencing (WGS) derived from NGS allows

for the rapid and precise identification of mutations linked to anti-TB drug resistance in previous clinical studies. In Indonesia, TB control has become a national health development priority. Despite notable progress over recent decades, TB continues to rank among the top four causes of mortality in the country. This literature review aims to present contemporary evidence regarding the efficacy and effectiveness of WGS in forecasting drug resistance in *Mycobacterium tuberculosis*.[2,3]

Methods

A comprehensive literature search was conducted across scientific databases such as PubMed, Scopus and Science Direct. The keywords used for literature search were "*Mycobacterium tuberculosis*", "Resistance", and "Whole genome sequencing". Research articles, clinical guideline, and meta-analysis were included. Inclusion criteria for this review are (1) published within the last 10 years, (2) published in English and Bahasa Indonesia, and (3) full text accessible. Literature review and result compilation was carried out by all authors.

Results and Discussion

Tuberculosis Cases in Indonesia

Globally, TB persists as a significant public health problem, with an estimated 9.9 million new cases reported in 2020. TB predominantly affects Southeast Asia, Africa, and the Western Pacific. Notably, Indonesia is among the top eight countries with the highest incidence rates, contributing to approximately 8.4% of global cases. This finding underscores the need for urgent, effective prevention and therapeutic measures, particularly in Indonesia. The World Health Organization (WHO) has recognized tuberculosis as a significant factor in morbidity and mortality, especially in low- and middle-income countries (LMICs), where socioeconomic conditions exacerbate its transmission.[4] Despite a gradual incidence rates decline globally, multidrug-resistant TB (MDR-TB) emerges as a formidable barrier to achieving elimination goals, with over 450,000 cases reported in 2012 alone.[5] In Indonesia specifically, TB continues to be a leading cause of death, exacerbated by challenges such as late diagnosis and inadequate treatment adherence. Recent studies indicate that while national efforts have been made to enhance TB control through improved diagnostics and treatment protocols, significant gaps remain in reaching vulnerable populations and ensuring comprehensive care (BMC Public Health, 2023). The interplay of urbanization, poverty, and healthcare access critically influences the epidemiological landscape of TB in Indonesia. As the country strives to align with the WHO's End TB Strategy, aiming to reduce deaths caused by TB by 90% by 2030, targeted interventions that address both medical and social determinants are essential for curbing transmission and improving health outcomes. Thus, understanding both global trends and local dynamics is of utmost importance in order to develop effective public health strategies in combating TB.[6]

Drug resistance in *M. tuberculosis*

Emerging drug-resistant strains of TB in hospitals and the community reveals various degrees of resistance, including rifampicin resistance (RR), MDR-TB, and extensively drug-resistant TB (XDR-TB). RR-TB is characterized by resistance solely to rifampicin, while MDR-TB involves resistance to at least isoniazid and rifampicin, the two most potent anti-TB medications. In 2017, approximately 558,000 RR-TB cases were documented worldwide, with 82% of this classified as MDR-TB. Treatment regimens for RR-TB and MDR-TB typically extend for 18 months or longer and involve a combination of selected first-line drugs along with various second-line agents, which tend to be more costly and associated with increased toxicity. Consequently, the management of these resistant forms of TB presents significant challenges in terms of treatment duration, adherence, and overall patient outcomes. The prolonged treatment necessary for effective management can lead to issues such as reduced patient compliance and heightened risk of adverse effects, further complicating the public health response to TB control efforts.[7]

Diagnosis of *M. tuberculosis* in Indonesia

The diagnosis of TB can be established based on clinical symptoms, physical examinations, bacteriological tests, radiological assessments, and other supporting examinations. Clinical symptoms of TB can be categorized into two groups: primary symptoms and additional symptoms. Primary symptoms may include a productive cough lasting for two weeks or more, while additional symptoms encompass hemoptysis, dyspnea, fatigue, loss of appetite, weight loss, night sweats, subfebrile fever persisting for over a month, and chest pain. When these symptoms are present and there are no available radiological or bacteriological facilities, a clinical diagnosis of TB may be made.[8]

Bacterial culture examination is considered the gold standard for identifying *Mycobacterium tuberculosis*. For clinical purposes, bacterial cultures are typically conducted using solid media, such as Lowenstein-Jensen, or liquid media, such as Mycobacteria Growth Indicator Tube (MGIT).[8]

Whole genomic sequencing (WGS)

WGS represents a major advancement in TB diagnostics, enabling analysis of over 90% of the genome compared to less than 1% with traditional methods prior to 2018. Gold standard method for DST is still phenotypic testing, despite significant challenges like the obtuse growth of *M. tuberculosis*, the need for advanced biosafety measures, and issues with reproducibility in the lab. As resistance in *M. tuberculosis* arises from genetic changes, new methods for detecting these genetic variations offer a potential solution for the rapid and standardized management of drug-resistant TB.[9,10]

Drug-resistant TB, driven by exposure to MDR and XDR strains, imposes major challenges to global control efforts, often exacerbated by delayed diagnoses and inadequate treatment. While rapid molecular techniques like GenoType MTBDRplus and Xpert MTB/RIF have emerged, their adoption is limited by cost and accessibility in low-resource settings. Since the first complete genome sequencing of H37Rv in 1998, WGS has demonstrated over 80% sensitivity and specificity in predicting

resistance to common anti-TB drugs, underscoring its potential to improve diagnostic accuracy and guide targeted treatments against drug-resistant TB.[9,10]

Effectiveness and efficacy of whole genomic sequencing

Currently, the advantage of the WGS system is that it can provide specific and detailed genetic information, allowing analysis of over 90% of genomic data, which leads to the comprehensive detection of all mutation related to drug resistance in tuberculosis patients.[11]

Compared to DST, WGS presents several important advantages including its ability to significantly shorten the diagnostic timeline, providing results in just 4 to 8 days compared to the weeks to months required for conventional culture methods. Additionally, WGS costs only around $80 each case, slightly lower than that of traditional DST, making it a more economical option.[9,12]

In past literature, WGS has proven to be highly effective for detecting drug-resistant TB, especially for first-line drugs, where it shows greater sensitivity and specificity than for second-line drugs. In a study by Katale *et al*. in Tanzania, WGS demonstrated strong agreement with traditional culture-based DST, with concordance rates of 81% for isoniazid (INH) and 97% for rifampicin (RIF). WGS also identified two patients with XDR-TB isolates confirmed by phenotypic DST, underscoring its value as a complementary tool to existing methods like GenXpert® MTB/RIF. Moreover, the specific mutations found in the *M. tuberculosis* genome can affect treatment outcomes; in the Tanzania study, 82.5% of participants achieved successful treatment, significantly higher than the global success rate for MDR-TB. These results highlight WGS as a promising method for enhancing diagnostic precision and treatment strategies, supporting efforts to eliminate TB by 2035.[13,14]

Whole genome sequencing and predictive accuracy in anti-tuberculosis drug resistance

The increasing phenomenon of MDR-TB and XDR-TB has prompted the application of WGS to predict drug susceptibility in cases of tuberculosis. First-line medications such as rifampicin (RMP) and isoniazid (INH) demonstrate consistently superior predictive accuracy compared to second-line agents. The fundamental genetic framework of resistance highlights the disparity, as primary drug resistance is primarily linked to well-defined and highly conserved mutations in specific genes, such as rpoB for RMP, or katG and inhA for INH. This basis results in a more distinct genotype-phenotype correlation.[15]

Second-line drug resistance, on the other hand, involves more heterogeneous and sophisticated processes, frequently involving several genes and regulatory pathways, confounding resistance prediction and reducing the sensitivity and specificity of WGS.16 This difficulty is exacerbated by insufficient resistance mutation databases and the presence of low-frequency or sub-clonal variants that might be undetected due to sequencing depth limitations, particularly for fluoroquinolones and injectable drugs.[17]

Methodological variables, such as variability in sequencing platforms and bioinformatics pipelines, lead to inconsistent predictive performance, with first-line medications showing more improvement in detection accuracy than second-line agents.[18] Furthermore, geographical variations in prevalent resistance mutations, as well as limited laboratory and bioinformatics capabilities in LMICs, may impede the generalizability and routine clinical use of WGS for predicting second-line drug resistance.[19]

Curent challenges and limitation of WGS for TB

The main challenge to acknowledge is that WGS requires advanced and specialized expertise and equipment. Implementing it into the national health system in a developing country would be expensive as it requires advanced support from the bioinformatics field and a continuous support from the country itself as implementing such an advanced program requires repeated growth and renewal.[9,11]

Unlike DST, which can determine the minimum inhibitory concentration (MIC) of drugs, WGS cannot provide this crucial information. This means that while WGS can identify genetic mutations associated with drug resistance, it may not fully capture the extent of resistance in certain cases. Moreover, there are instances where TB strains exhibit drug resistance without any detectable genetic mutations, which can lead to false assumptions about their susceptibility.[10,20]

Another challenge with WGS is related to strain selection bias and the limited number of resistance candidate genes that are currently understood. This can result in relatively low predictive sensitivity for certain drugs, making it less reliable in some scenarios. Additionally, the definition of XDR-TB was updated in January 2021, highlighting the need for ongoing adjustments and observations regarding how well WGS can predict resistance patterns.[9,10]

Conclusion

WGS presents a transformative approach to TB diagnostics by providing rapid and detailed insights into drug resistance patterns. Compared to traditional DST, WGS significantly shortens diagnostic timelines and reduces costs while offering a broader analysis of genetic mutations. Studies have demonstrated its capacity to guide targeted treatment strategies as well. In Indonesia, which ranks among the top contributors to global TB cases and deaths, WGS could fill critical gaps in tailored treatment, essential for combating the country's high burden of multidrug-resistant TB.

However, implementing WGS in Indonesia presents significant

challenges. Limited healthcare infrastructure, socio-economic disparities, and the need for specialized expertise and bioinformatics support make nationwide adoption difficult. Furthermore, WGS also faces issues with incomplete resistance data. Despite these hurdles, integrating WGS into Indonesia's TB control programs, with strategic investment and capacity-building, could strengthen diagnostics and accelerate progress toward End TB Strategy goals from the World Health Organization.

ADDITIONAL INFORMATION

Data availability statement

All data used in this study were obtained from previously published articles and publicly accessible scientific databases. No new datasets were generated or analyzed during the current literature review.

Conflict of Interest

The author declares that there is no conflict of interest related to the publication of this article.

Author Contribution

The author was responsible for the study conception and design, literature search, data extraction, analysis and interpretation of the findings, as well as manuscript drafting and final approval of the version to be published.

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