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Harnessing Bioinformatics to Decode Drug Resistance and Guide Vaccine Design in Mycobacterium tuberculosis

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ABSTRACT

Mycobacterium tuberculosis presents a major challenge to global health due to tuberculosis (TB), which is worsened by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. This study provides a thorough examination of bioinformatics research, highlighting how the integration of genomic, proteomic and metabolomic data into TB research has revolutionised the way TB is studied, particularly in understanding resistance mechanisms, identifying new therapeutic targets, and expediting the development of diagnostic tools and vaccines. Whole-genome sequencing (WGS) and newer technologies like Oxford Nanopore Technologies (ONT) have since paved the way to the rapid identification of strain-specific mutations, with novel bioinformatics tools like PhyResSE, Mykrobe and GBOOST offering a powerful platform in mutation profiling, resistance prediction and strain classification. Furthermore, resistance prediction is also being transformed by machine learning and AI-based models, which improve the accuracy of clinical choices and monitoring options. Epitope prediction, molecular docking, and analysis of population coverage to inform the selection of promising immunogenic candidates are also proposed in the study as an in silico pipeline of rational vaccine design. Although continued efforts at infrastructure, standardisation, and workforce training are always ongoing in many settings where this is still seen as a major issue, especially in high-burden settings, this paradigm shift in an interdisciplinary approach is a clear indication of progress in the fight against one of the most prevalent and persistent infectious diseases in the world.

Keywords: Bioinformatics, Drug resistance, Epitope-based vaccine design, Tuberculosis genomics.

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1. Introduction

1. 1. *Mycobacterium tuberculosis's* Global Health Impact

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis and is one of the most dangerous infectious diseases in the world. TB is one of the key health challenges that are faced globally, mainly because of the high mortality rates in developing countries. The infection spreads through respiratory droplets and is difficult to contain, especially with the emergence of drug-resistant strains. Recent developments include the emergence of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) strains, which are difficult to treat, in addition to acting as a fast spreader of the epidemic. Studies have shown that one of the main factors behind further infection and mortality rates is antibiotic resistance, leading to the failure of conventional interventions and increased spread of the populations (Couvin et al., 2025). This issue poses a global health challenge and requires innovative interventions that integrate biology and computational sciences to improve treatment and diagnostics. Also, TB has a significant health system burden and is a major drain on national economies, particularly where healthcare infrastructure is weak (Acharya et al., 2020). The World Health Organization (WHO) Global Tuberculosis Report 2023 states that in 2022, TB claimed 1.3 million lives and infected 7.5 million people worldwide, ranking it as the second deadliest infectious disease after COVID-19.

1. 2. Bioinformatics Contribution in the Study of *M. tuberculosis*

Bioinformatics is the use of information technology, especially computational methods, in the collection, analysis and interpretation of biological information, particularly genomic and proteomic sequences. Innovations in genomics and biological databases have bridged knowledge gaps in *M. tuberculosis* biology and genetic differences. Whole-genome sequencing (WGS) of M. tuberculosis has opened new opportunities in the study of the genetic makeup of various forms, which has led to a better understanding of biology as well as resistance to drugs. Bioinformatics tools play an important part in the identification of the mutations that are associated with drug resistance and in the identification of the potential drug targets, including proteins involved in resistance or virulence (Sola et al., 2001). Additionally, the combination of genomic data with proteomics has greatly benefited research on such complex microorganisms as *M. tuberculosis*, providing both pangenomic and proteomic global perceptions to design strategies focused on diagnosis, therapy, and vaccine development (Alaridah et al., 2019).

1. 3. Objectives and Scientific Significance of the Research

This paper addresses research investigating the potential of bioinformatics technologies in fighting TB, especially with the increasing cases of drug-resistant strains. The main aim is to attain a combined perspective of the genome and proteome of M. tuberculosis in order to discover new resistance mechanisms and identify effective drug targets which will be harder to resist in future. Genomic and proteomic platforms can be used together to develop a superior platform for developing specific solutions, such as diagnostics that are faster and the development of new vaccines that offer better preventive measures (Bakuła, Dziurzyński, et al., 2023). Moreover, the study also points out discoveries in the field of diagnosis, treatment, and vaccine development using modern computational analysis, claiming that it may be an effective tool for overcoming the current difficulties that TB and its resistance cause (Rosenthal et al., 2017). This article is a narrative review which summarizes literature from PubMed, Scopus, and Web of Science with the following keywords: bioinformatics, tuberculosis, drug resistance, genomics, vaccine design, and machine learning.

2. Methods of Genome Sequencing and M. tuberculosis Data

2. 1. Technologies of Genetic Sequencing Utilised

Genome sequencing has made exponential strides in recent years, resulting in the fast and accurate retrieval of complete genomes of *M. tuberculosis* strains. Some of the revolutionary methods include technologies like WGS and ONT. ONT offers long-read sequencing, which simplifies the identification of tricky genetic mutations, especially in repetitive genomic regions that were previously inaccessible to short-read sequencing technologies. Moreover, ONT minimizes the time of analysis and diagnosis of drug resistance and response to treatment, which enables the process to take hours instead of weeks (Bellad et al., 2022). Contemporary sequencing matches volume with quality, as data quality evaluations aim to obtain definitive genetic data. These developments allow for the rapid and accurate identification of drug-resistant strains through identification of resistance-linked mutations (Bogaerts et al., 2021).

2. 2. Bioinformatics Software and Tools for Genomic Data Analysis

Bioinformatics tools are important and are used in interpreting sequencing data of *M. tuberculosis*. They are used for mutation detection, strain classification and epidemiological studies. Among the well-known tools are PhyResSE, which has an intuitive interface, allows the use of high-grade sequence data, and maintains offline functionality; and Mykrobe, which also has the possibility of offline usage and an intuitive interface to distinguish bacterial species and drug resistance (Cancino-Muñoz et al., 2022). SpolPred software can predict strain types directly in raw sequence reads with higher speed and accuracy than assembly-based strategies, allowing both phylogenetic and epidemiological classification (Chen et al., 2022). Targeted databases such as MUBII-TB-DB contain resistance-related mutations and their biological explanations and help in effective targeting and surveillance of resistance that is evolving (Bakuła, Marczak, et al., 2023). **Table 1** presents bioinformatics tools used in genomic analysis.

Table 1. Major Bioinformatics Tools Used for Genomic Analysis of M. tuberculosis.

Tool	Main Function	Algorithm/ Method	Input Data Type	Output	Key Features
PhyResSE	Prediction of drug resistance and lineage identification	Reference-based mutation analysis	Raw reads or assembled genomes	Resistance profile and lineage classification	Web-based interface and curated mutation database
Mykrobe	Species identification and drug resistance prediction	De Bruijn graph approach	Raw reads	Drug susceptibility prediction	Rapid analysis and offline capability
SpolPred	In silico spoligotype determination	Spoligotyping algorithm	Raw reads	Strain classification	Fast and highly accurate strain typing

TB-Profiler	Detection of resistance mutations and lineage assignment	Mapping-based variant calling	Raw reads	Drug resistance report and lineage information	Supports MDR/ XDR prediction and comprehensive mutation database
MTBseq	Whole genome sequence analysis	Reference-guided SNP analysis pipeline	Raw reads	SNP identification, phylogeny, and resistance profile	High-resolution genomic analysis
FastQC	Sequence quality assessment	Statistical quality control analysis	Raw reads	Sequence quality reports and metrics	Detection of low-quality reads and GC bias
BaseClear pipeline	Genome assembly and variant analysis	Hybrid assembly and mapping approaches	Raw reads	Genome assembly and SNP detection	Suitable for large-scale sequencing projects
MUBII-TB-DB	Annotation of resistance-associated mutations	Database-driven mutation annotation	Assembled genomes and mutation lists	Functional interpretation of mutations	Curated resistance mutation database

A three-dimensional visualisation of the workflow of the pipeline needed in tuberculosis research, which involves all parts of clinical sampling, genome sequencing, bioinformatics systems, and AI-powered prognoses to assist in the diagnosis, therapeutics of the disease or its cure, and disease surveillance, is illustrated in **Figure 1.**

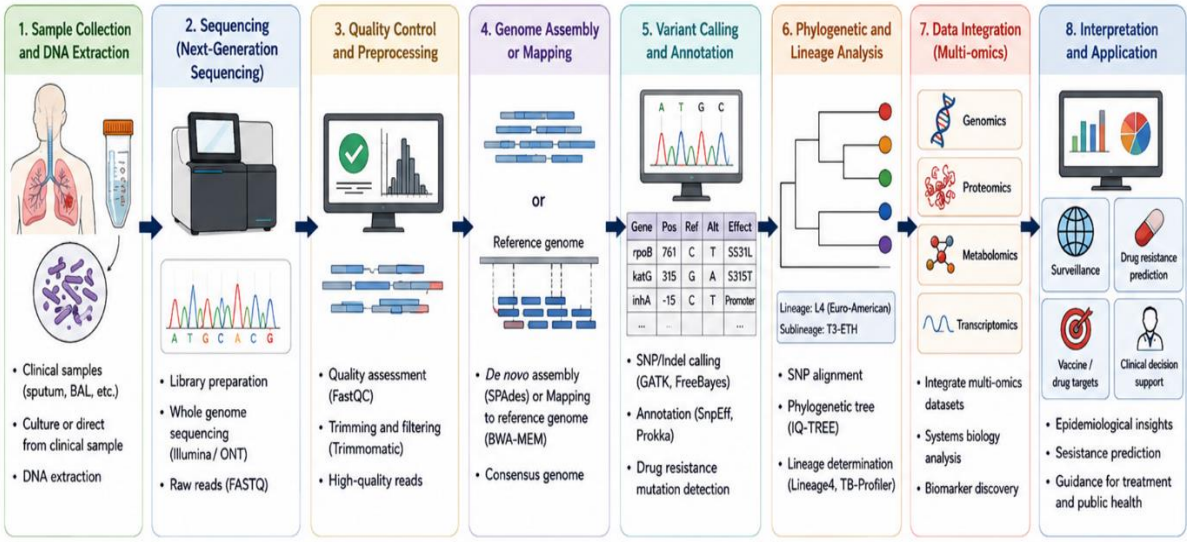

Figure 1. Integrated Bioinformatics Pipeline for *M. tuberculosis* Analysis.

2. 3. Challenges and Opportunities in Clinical and Epidemiological Application of Genome Sequencing

Genome sequencing has witnessed great progress, but its application in clinical and epidemiological practice still has difficulties. These weaknesses are related to the trouble detecting resistance caused by mutations that are not known or by an emergence of new mechanisms. It is also equally inaccurate to distinguish between true resistance-associated mutations and neutral variants. However, there are prospects for expanding early detection through a combination of sequencing data with proteomics and multi-dimensional data, such as gene and protein expression, as well as increasing the detection capacity of resistant cases and monitoring disease outbreaks (Puustinen et al., 2003). The scope of multilayered data analysis creates new horizons in the knowledge of the process of adapting bacteria to antibiotics and creating prescribed treatments (Couvin et al., 2020).

3. Drug Resistance-Associated Mutation Analysis of M. tuberculosis

3. 1. Major Genes that Participate in Antibiotic Resistance

The major relationship between drug resistance in *M. tuberculosis* and mutations in certain genes lies in their role as important targets of antibiotics. The key among them are rpoB (rifampicin resistance), katG and inhA (isoniazid resistance), gyrA (fluoroquinolones resistance), and pncA (pyrazinamide resistance) genes. These genes influence bacterial survival by changing the structure of drug targets, thereby making antibiotics less effective. It is also important to note that such mutations as the one at codon 531 in rpoB are powerful indicators of rifampicin resistance and these are among the most frequently reported mutations associated with treatment failure. The importance of comprehending interactions between several mutations lies in the fact that synergetic effects may establish a complex pattern of resistance that restricts therapeutic options (Gautam et al., 2018). A 3D image of the major areas of resistance genes (rpoB, katG, inhA, gyrA, pncA), the most frequent associated mutations causing drug resistance in tuberculosis, and also their connection to corresponding antibiotics is shown in **Figure 2**.

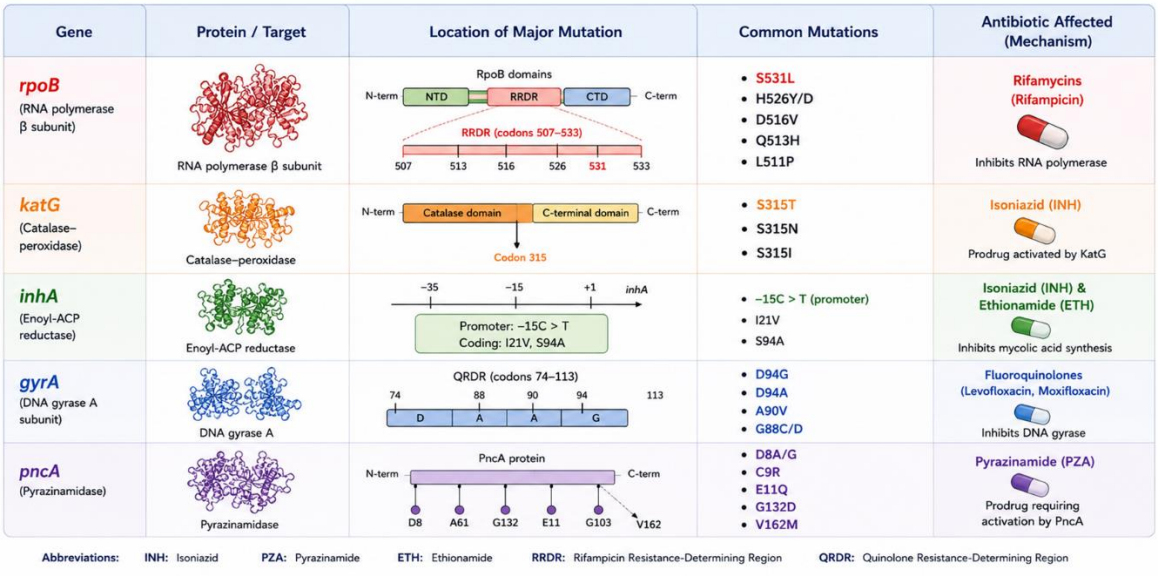

Figure 2. Major Genes Associated with Antibiotic Resistance in *M. tuberculosis*.

3. 2. Bioinformatics Methods of Detecting and Analyzing Simultaneous Mutations

Single mutations do not usually cause resistance but interactions between multiple mutations of the genes or SNP pairs. More advanced bioinformatics methods, such as GBOOST, can examine such confounding interactions to identify gene-gene combinations that lead to resistance patterns that cannot be explained by single mutations. These studies have also highlighted

the importance of gene families such as PPE proteins, which could have a remote effect on resistance and bacterial adaptation to drug pressure, thereby aiding in the improvement of resistance estimation and precision therapy methods (Katale et al., 2020).

3. 3. Predicting Drug Resistance Using Computational Models and Machine Learning

Due to the complexity of genetic resistance, machine learning models have become a powerful method for analysing genomic data and can assess a resistant strain with higher precision than mutation detection governed by rules. The prediction of resistance to various anti-TB drugs is enhanced through the use of algorithms like neural networks and support vector machines, which enhances sensitivity and specificity. Such models will be able to identify multidimensional genetic data resistance patterns, including unseen or compound patterns that offer greater scope of prediction and less human error. Such a method is promising to be used clinically and epidemiologically in surveillance and customised interventions (Guyeux et al., 2024; Lam et al., 2021).

A schematic diagram of the epitope-based vaccine development pipeline composed of antigen selection, epitope prediction, the analysis of the population coverage, molecular docking and the in silico validation considering three dimensions is illustrated in **Figure 3**.

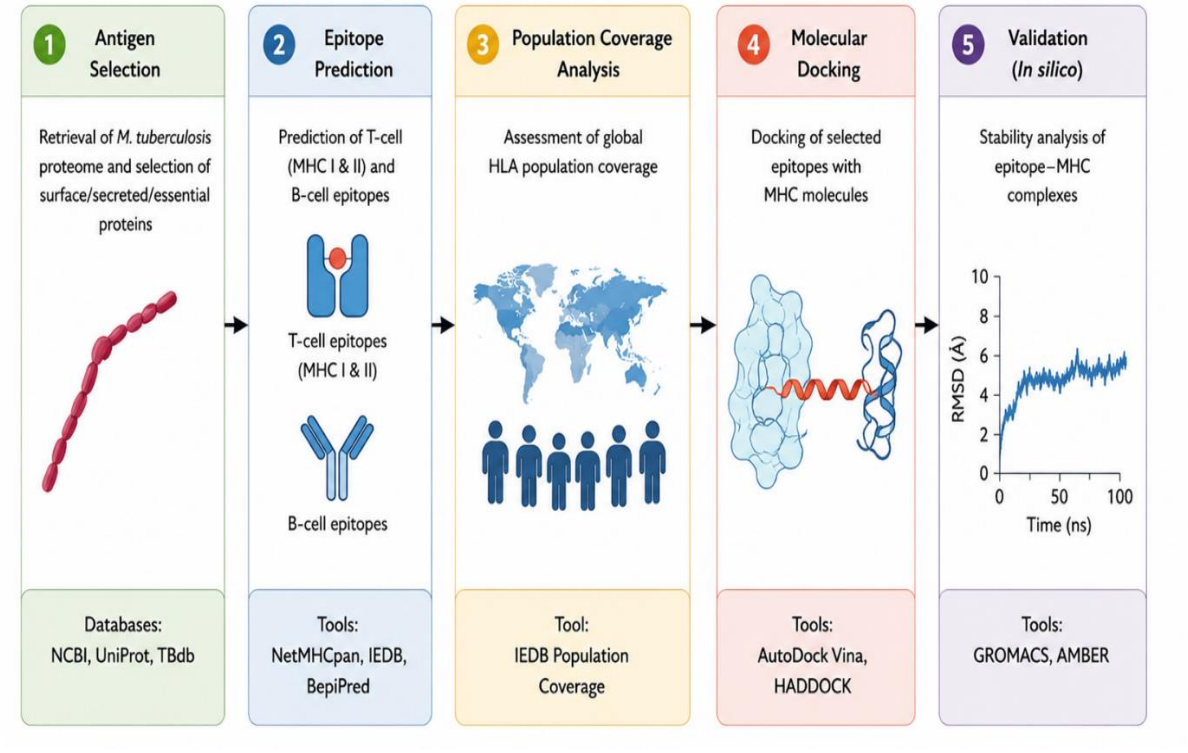

Figure 3. *In Silico* Pipeline for Epitope-Based Vaccine Design Against *M. tuberculosis.*

4. Bioinformatics and Proteomic Applications to Study *M. tuberculosis*

4. 1. *M. tuberculosis* Proteomics Research

Proteomics plays a very important part in offering vital information about proteins that play roles in bacterial resistance mechanisms and pathogenicity. The methods to study new resistance-associated proteins and proteins that help bacteria to survive within hosts can be identified using such techniques as mass spectrometry. This kind of knowledge can aid in finding drug targets and vaccine contents. In vivo and in vitro proteomic analyses during drug and immune challenges provide a memory of unknown bacterial adaptive strategies and resistance mechanisms (Couvin et al., 2025). Combining proteomics and genomics improves insights in the cellular architecture and functions of bacteria (Alaridah et al., 2019).

4. 2. Molecular Structure of Major Proteins as Targets of the Drugs

X-ray crystallography, among other methods, is a structural study that has led to the elucidation of the 3D structure of key proteins such as diaminopimelate decarboxylase (DAPDC), which is critical for lysine biosynthesis and bacterial survival. Knowledge of structural regions and binding sites contributes to the design of inhibitors of these proteins. Other complexes with toxin-antitoxin complexes, like VapBC, that control growth and persistence are also studied, where bioinformatics tools can be used to identify and target interaction sites for therapeutic intervention (Guyeux et al., 2021; Hatherell et al., 2016).

4. 3. Protein Structure Prediction and Genetic Modifications via Computational Simulations

Computational simulations model the influence of genetic mutations on the structure and function of proteins together with the sites and strengths of drug binding. They help in the interpretation of resistance mechanisms at a molecular level by predicting dynamic changes because the movement of mutation can also be achieved. The use of molecular dynamics with the help of machine learning allows narrowing down predictions about protein-drug interactions further, thus enabling rational drug design against resistant strains (Lam et al., 2021; Zhang et al., 2023a).

5. Design of Vaccines against Tuberculosis with the Help of Bioinformatics

5. 1. Contemporary Vaccine Plans and Multiple-Dose Vaccination Plans

Despite more than a hundred years of use, the *Bacillus* Calmette-Guerin (BCG) vaccine still shows low efficacy, especially in cases of pulmonary TB in mature individuals. Bioinformatics in vaccine design provides ample scope to use the whole proteome and pick numerous epitopes to generate broad immune responses in modern vaccine designs. Multi-dose epitope-selected vaccines are designed to generate cellular and humoral immunity, which enhances long-remembered defenses and minimizes evasion by immune bacteria. Vaccines can be supplemented by immune adjuvants which boost their effectiveness (He et al., 2020; Zhang et al., 2023b).

5. 2. Prediction and Immunological Evaluation with Computational Resources

Scholars employ tools of epitope prediction, molecular docking, and molecular dynamics simulation to determine the parts of peptides that might create an immunologic response. The tools used to predict Major Histocompatibility Complex (MHC) binding assist in the selection of potential peptides. Examples include peptides from the EsxG-EsxH and Rv3587c complexes, which have demonstrated *in silico* potential as vaccines, exhibiting immune activation and blocking bacterial entry into host cells (Chisompola et al., 2021; Hussien et al., 2022).

5. 3. The Challenges of the Future in TB Vaccine Improvement and Development

Genetic variability of *M. tuberculosis* strains is a problem as far as wide-coverage vaccination is concerned. Although bioinformatics can make the process of searching for vaccine candidates faster and epitope selection easier, extensive clinical testing is required before confirming the safety and efficacy of the vaccine in humans. It is essential to incorporate computational prediction and experimental immunology. A contributing factor to future success is the continued improvement of algorithms to streamline epitope selection and enhance vaccine formulations (Rosenthal et al., 2017).

6. Role of Biological and Metabolomics Analyses in Tuberculosis Research

6. 1. Advanced Protein and Metabolite Profiling in *M. tuberculosis*

Metabolomics supplements proteomics due to the proficiency of small-molecule bacterial and host metabolites during infection. The approach allows the identification of biomarkers that can be adopted to diagnose TB, distinguish between latent and active infections, and guide treatment. Although the results are good, the complex data of metabolomics require strong bioinformatics to analyse and to validate biomarkers suitable for clinical practice (Alaridah et al., 2019; Jajou et al., 2019).

6. 2. Tuberculosis and the Microbiome Interactions

Respiratory tract microbiota studies through 16S rDNA-based sequencing have yielded a change in the microbe population of the TB patients, as compared to the healthy members. An increased abundance of genera such as Cupriavidus and Porphyromonas in the sites of lesions demonstrates potential roles either as cofactors or contributors to the pathogenesis or secondary infections of TB. To study host-pathogen-microbiome interactions, bioinformatics tools come in handy in the analysis of microbial diversity (A. Dawood & Alnori, 2020). Critically, changes in the respiratory microbiota with TB can affect host immune function and cellular metabolism. Altered microbial metabolites resulting from symbiosis can impact macrophage activation, lipid metabolism, amino acid biosynthesis and inflammatory signaling pathways to establish a metabolic niche that promotes the persistence and progression of *Mycobacterium tuberculosis*. A combination of microbiome data with metabolomics and transcriptomics could offer a greater understanding of the interaction between host and microbe and help to identify new biomarkers and drug targets for TB.

6. 3. Leveraging of Multi-Omics Data to Research on Biological Interactions

Combining multi-omics data, i.e., genomic, proteomic and metabolomic data, makes it possible to take a host-microbe interactome during TB infection and progression into account comprehensively by modelling it. Such complex data are analyzed using cutting-edge computational techniques such as artificial intelligence to unveil biologically relevant models that can be inaccessible by conventional methods. These understandings are utilized in the development of specific preventive and treatment approaches at different stages of the disease (Kargarpour Kamakoli et al., 2020; Morey-León et al., 2023).

7. Computational Modelling and Viral Surveys *M. tuberculosis* Study

7. 1. GenH Networks and Toxin-Antitoxin Systems

The toxin-antitoxin (TA) systems, including the VapBC system of *M. tuberculosis*, control bacterial growth arrest, adaptation to stress, and dormancy. Bioinformatics and structural analyses show the mechanisms of interaction between toxin and antitoxin moieties, which is crucial to the regulation of survival of the bacteria in an environment that is not accommodating. Computational models of various scenarios of survival provide possible options for biotechnological interventions of disrupting TA systems as antimicrobial measures (Hatherell et al., 2016; Moco et al., 2022).

7. 2. Functional Prediction of M. tuberculosis Proteins

The structural modelling methods are used to identify the active and binding active sites of proteins that are associated with drug resistance, explaining the effects of genetic mutations on molecular activity. The integration between genetic and functional studies leads to rational drug target discovery and is the basis for discovering drug interaction sites, which are important in the development of next-generation anti-TB drugs (Genestet et al., 2022; Leong et al., 2022).

7. 3. Simulations in the Development of New Drugs

The binding interactions between proteins and drugs, as well as the impact of mutations on binding affinity and stability, are investigated by the means of molecular dynamics simulations. These experiments fulfil the resistance mechanisms and estimate the efficacy of the drugs under study. Computational methods accelerate drug discovery by pre-evaluating molecular interactions before involving them in costly tests in a lab (Kohl et al., 2018; Lam et al., 2021).

8. Machine Learning and Artificial Intelligence in Diagnosis and Monitoring of TB Infections

8. 1. Machine Learning Model Formulation

Machine learning algorithms increase the sensitivity and speed of identification of drug-resistant *M. tuberculosis* using genomic data. Whereas rigid rule-based tests are rather insensitive in the classification of resistant strains, the models are sensitive in the classification of resistant strains compared to the rule-based test. These models enable predicting resistance to multiple drugs simultaneously. Machine learning is becoming an irreplaceable part of TB surveillance and clinical decision-making at the global level (Guyeux et al., 2024; Haft et al., 2024).

8. 2. The Use of Computational Tools to Speed Vaccines/Drugs Development

Artificial intelligence (AI) is used to process huge genomic and proteomic data to select interesting drug and vaccine targets. Molecular modelling using AI is used to predict host-pathogen interactions and to assess the work of vaccines on them, which can save development time and cost significantly. In recent years, these technologies have exhibited significant improvements in the identification of proteins that trigger the best immune responses and in the facilitation of successes of TB control programmes (Tafaj et al., 2020; Zhang et al., 2023a).

8. 3. Hidden Value and Difficulties of Applying AI in TB Healthcare

Implementation of AI in clinical laboratories enhances the speed of data processing and healthcare system reaction. Nevertheless, issues such as regulation, privacy, and reliability come into play. Specific training of staff and modernization of infrastructure are critical measures that could ensure the effective integration of AI into the TB diagnosis and treatment guidelines (Kargarpour Kamakoli et al., 2020; Morey-León et al., 2023).

9. Future Directions and Research Trends in Bioinformatics for TB

9. 1. Innovations in Genomic Data Collection and Analysis

This changing trend is also characterized by the move to next-generation sequencing (NGS) technology to produce multi-layered genomic and proteomic data. Collaboration has resulted in the merging of datasets to pursue a more comprehensive understanding of bacterial biology and bacterial host interactions. The introduction of new tools incorporating artificial intelligence and cloud computing also allows sophisticated, easy-to-use data analysis and even continuously updated databases of genomes with the most recent results (Mekonnen et al., 2023).

9. 2. Combination of Bioinformatics and Epidemiological Research/Disease Surveillance

Whole-genome sequencing also enables accurate monitoring of transmission dynamics and the occurrence of mutations in TB. Sophisticated databases and open systems allow data sharing worldwide and collaborative epidemiologic research that helps in a timely response to outbreaks and the conduction of a set of public health programmes (A. A. Dawood, 2024). The models built on this integration are predictive, which allows managing the spread of diseases and maximizing the quality of healthcare.

9. 3. Technical and Applied Problems of Implementing Bioinformatics Results

However, a high potential is accompanied by obstacles, such as making data sources and methods of data analysis standardised across borders. Infrastructure and skilled workforce do not develop in low-income regions because of scarce resources. To overcome these gaps, policies should work to facilitate sustainable investments, cross-country collaboration, and lifelong learning to build upon and bolster bioinformatics-assisted TB research and clinical practice (Bakuła, Dziurzyński, et al., 2023; Yin et al., 2023a).

10. Conclusion and Recommendations for Future Research on *M. tuberculosis* and Bioinformatics

10. 1. Summary of Current Bioinformatics Achievements in TB Research

Research on *M. tuberculosis* has undergone a revolution with bioinformatics due to the fact that knowledge about genome complexity, drug resistance mechanisms, diagnosis, and treatment mechanisms has been significantly fast-tracked. Genomics, proteomics, and computational sciences have been integrated to provide new solutions and to improve outcomes in TB control. The developments in the field of sequencing, the analysis of mutation, and the designing of vaccines would be both a major step forward and a bright hope for the populations affected by them around the world (Couvin et al., 2025; Yin et al., 2023b).

10. 2. The Potential Role of the Emerging Technologies in TB Control

Trends in the future point to the increasing application of AI and machine learning in the creation of fast, sensitive diagnostic methods and in the resolution of intricate genetic patterns of resistance. Such technologies are capable of managing large amounts of data and displaying real-time, actionable insights that can make the decisions of healthcare providers more evidence-based. Avant-garde, data analytics-assisted, collaborative, cross-disciplinary research regimes are likely to facilitate international TB control activities (Chesov et al., 2022; Guyeux et al., 2024) .

10. 3. Recommendations for Research and Health Policy

Investments in bioinformatics infrastructure and technologies through sustainability are very important and required mainly among the high-burden countries. International data sharing and the utilization of open bioinformatics tools should be promoted by health policies so that effective responsive solutions can be developed. Training of clinicians and researchers and continuous development of skills are vital factors that will lead to the success of this multidisciplinary model in TB research and care implementation (Bakuła, Dziurzyński, et al., 2023).

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data Availability

No data was used for the research described in the article.

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