Artificial intelligence in tuberculosis: a new ally in disease control

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Shareable abstract (@ERSpublications)
TB is an important threat to public health, but AI may bring new insight and capabilities to the problems faced. Prioritising data quality will be key for the success of the fourth industrial revolution in TB disease control. https://bit.ly/4cWpkPU

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Abstract

The challenges to effective tuberculosis (TB) disease control are considerable, and the current global targets for reductions in disease burden seem unattainable. The combination of complex pathophysiology and technical limitations results in difficulties in achieving consistent, reliable diagnoses, and long treatment regimens imply serious physiological and socioeconomic consequences for patients. Artificial intelligence (AI) applications in healthcare have significantly improved patient care regarding diagnostics, treatment and basic research. However, their success relies on infrastructures prioritising comprehensive data generation and collaborative research environments to foster stakeholder engagement. This viewpoint article briefly outlines the current and potential applications of advanced AI models in global TB control and the considerations and implications of adopting these tools within the public health community.

Introduction

Tuberculosis (TB) is a persistent global health challenge, with 7.5 million new diagnoses and an estimated incidence of 10.6 million cases in 2022 [1]. At present, achieving the World Health Organization (WHO) End-TB Strategy's ambitious aims for a 95% decrease in TB-related deaths and a 90% decline in TB incidence rate by 2035 appears unrealistic [2].

The status quo of TB control methods is fraught with challenges. The standard passive case-finding strategies fail to identify non-symptomatic infectious individuals with pulmonary TB, who represent a large proportion (50.4%) of the overall disease burden, thereby hindering effective interruption of transmission [3]. The tuberculin skin test and interferon-γ release assays, which are essential diagnostic tests for sensitisation against *Mycobacterium tuberculosis* antigens, cannot distinguish between latent infection or previous disease [4].

Current treatment regimens for adult drug-susceptible and drug-resistant TB are long, can result in serious drug-related adverse health events, and represent a significant financial burden to patients [1]. Previous efforts to reduce the duration of current regimens resulted in increased risk of treatment failure and

relapse [5]. In addition, the inherent technical challenges of sputum culture-based treatment monitoring complicate accurate patient follow-up in both programmatic and clinical trial settings, and are not applicable in paucibacillary populations.

The increased prevalence of multidrug-resistant and extensively drug-resistant strains, and the emergence of bedaquiline resistance, represent grave public health concerns and threaten to decrease rates of successful treatment [1]. The deficits in current diagnostic, treatment and vaccination capabilities are clear; urgent solutions are required if hopes for achieving the WHO End-TB targets are to be maintained.

Artificial intelligence (AI), heralded as the technology underpinning the fourth industrial revolution, has resulted in paradigm-shifting breakthroughs in a variety of scientific disciplines, including healthcare. Machine learning (ML) and deep learning (DL), subdivisions of AI, are distinguished by unique model architectures and their methods for processing the characteristics, or "features", of the input data. The differences between ML and DL are expanded upon in figure 1 [6].

ML models can learn patterns from data and apply them in novel settings but involve human-based feature engineering; raw data requires modification before input, which is time-consuming and demands high levels of field expertise. This can be circumvented with DL-based models, which receive raw input data without prior modification and generate new "intermediary" features from the raw input, permitting the discovery of novel representations of features and, thereby, new patterns in the data [7]. The impact of these tools in healthcare has been remarkable [6] but has caveats. Reaping the full benefits of such powerful tools requires large and comprehensive datasets for model training. This prerequisite is easily achieved in diseases such as cancer but is not as straightforward for TB. Despite this, there have been exciting developments in AI implementation within TB disease control; for example, computer-assisted diagnostic (CAD) algorithms for TB radiography analysis [8] and DL models designed to predict mechanisms of antimicrobial resistance [9].

In this viewpoint, we present the opportunities where AI could be deployed to address the current issues within TB disease control, and also seek to open a discussion of the future perspectives within the field in light of the opportunities afforded by AI, including the associated challenges.

AI in the clinical setting

Diagnostics

The field of diagnostics was recently described as "the weakest link in TB disease control" [10]. However, it is also the area in which the most significant contributions from AI-based tools have been achieved.

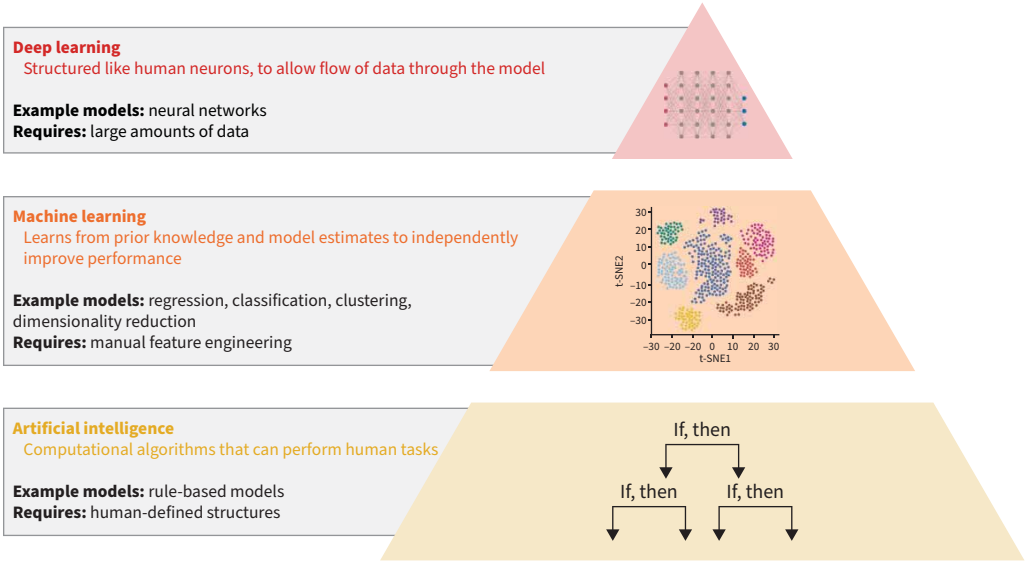

FIGURE 1 Artificial intelligence, machine learning and deep learning hierarchy, with example models and requirements. t-SNE: t-distributed stochastic neighbour embedding. Figure created in BioRender.

In addition to some algorithms achieving sensitivity measures on a par with human experts (95.5%) [8], implementation as standalone triage tools and with molecular diagnosis *via* nucleic acid amplification techniques appears highly cost-effective [11]. WHO recommendations now include the use of CAD algorithms for diagnosis where human experts are unavailable [12].

This has been possible in part by the use of radiography as a primary diagnostic tool for TB [13], resulting in large volumes of radiographic imaging data available for model training, that have permitted the formation of a range of datasets from patients across areas of high endemicity [14].

However, the requirement for expert labelling of these data points prior to model development presents a significant barrier for researchers and public health professionals within low-resource settings. Transfer learning and semi-supervised techniques could avoid requirements for labelled data in the future [15], but examples from open-access initiatives, such as the VinDr-CXR dataset [16], demonstrate the power of concerted data aggregation and collaborative data sharing efforts in the advancement of disease control.

AI in treatment

In TB, treatment success on standard of care regimens is high (~88%) [1]. However, those patients at risk of long-term outcomes like relapse and those that will suffer adverse treatment outcomes cannot currently be stratified at baseline for alternative supportive therapies.

Prognostic determination of treatment outcome has resulted in significant improvements to patient care, particularly in oncology [17]. Within TB, any improvements in treatment strategy must balance overtreatment rates and management of the risk of adverse outcomes, including drug-induced injury and disease relapse. Exciting work from Imperial *et al*. [18] created a patient stratification framework for optimised treatment duration based on markers of baseline disease severity by employing traditional statistical modelling methods, and extension of this into ML modelling has produced a range of models designed to predict treatment failure [19–22] and adverse events [23, 24]. The models incorporate a range of data types, including clinical covariates like age and sex, and also transcriptomic gene signatures. Notably, there is a visible gap between the creation of these models and their translation into clinical practice, principally due to a generalised lack of validation in external datasets, and heterogeneity in the included features, resulting in a wealth of standalone algorithms that did not translate directly to clinical practice [25].

Exemplified in the case of diagnostic models based on radiographic image data, collaborative data generation and sharing efforts would provide platforms through which these disparate models could be systematically validated, hopefully improving rates of adoption into clinical practice. Another avenue is the integration of data types into multimodal signatures; these types of ML models have demonstrated superior performance to those based on unimodal data in other diseases [26] and TB [27].

AI in research

There are currently 28 antitubercular compounds in phase I–III trials, 18 of which are novel [28]. The complexity of the *M. tuberculosis* organism is a significant hurdle in the rate of identification and development of novel compounds [29]; deployment of ML methods for the large-scale screening [30] and compound prioritisation processes [31] stands to streamline the TB drug development pipeline and provide a novel tool in efforts to overcome drug resistance.

The recent advances in basic research into host–pathogen interactions are exciting examples of the insights available in TB research following investment in complex data generation. Improved resolution of the underlying cellular dynamics of disease and treatment response has been made possible in a range of infectious diseases by novel molecular techniques like single-cell multi-omics. The high-dimensional datasets produced by these methods are rich opening avenues for novel drug target pathways or host-directed therapies [32]. However, these data require powerful neural networks to extract meaningful biological signals [33]. Initial application of these methods in TB has provided insights into long-term memory T-cell behaviour [34], identified novel immune cell subpopulations across infection states [35], and expanded on the concepts of pretreatment patient classification [36].

Opportunities, considerations and future perspectives

Although the potential advances afforded by AI-based analysis tools are considerable, attitudes within the medical community towards AI remain an important facet of the discussion. Natural language models, a type of DL model incorporated for automating administrative tasks for clinicians and nurses, resulted in savings in working hours of 17% and 51%, respectively [37]. However, varied perceptions of the true

extent of AI model capabilities have been reported. There are established concerns from healthcare workers regarding the accuracy of AI-based clinical decision algorithms and the perceived loss of professional autonomy. Negative attitudes towards AI and an observed lack of direct clinical translation are compounded by the prevalence of "black-box" model architectures [38]. Two key factors of model design contribute to this issue: accuracy and interpretability [39].

Black-box architectures, in which sacrifices in algorithm interpretability are made for increased accuracy, pose obvious problems in patient-centred approaches and weaken trust from healthcare providers, as it becomes difficult to determine how diagnostic decisions are achieved and their clinical relevance. Solutions have arisen from tools such as Grad-CAM [40], which are designed to include increased interpretability of convolutional neural network architectures used for image data analysis.

Concerns regarding the propagation of racial bias in algorithm development are established and central to the discussion of AI in healthcare [41]. However, studies examining the intersection between model interpretability and bias propagation within computer-assisted clinical decision-making are now highlighting the further nuances of this problem, concerning physician over-reliance on model output. Using a case study of respiratory failure diagnosis, Jabbour *et al.* [42] demonstrated that while the greatest diagnostic performance was achieved by physicians plus interpretable model support, incorrect model interpretations significantly worsened diagnostic accuracy, even to below the performance of the physician alone. The results of this work are summarised in table 1.

What is important to note is that the accuracy of physicians' interpretations was highest when accompanied by accurate, interpretable AI tools. This also suggests important considerations for future collaborations between ML engineers and healthcare professionals; that there should be a concerted focus on model integration workflows that maintain and encourage physician autonomy with additional theoretical training concerning model functionality.

Conclusions

As outlined above, the issues in TB control are multifaceted. Diagnostic tools that increase our capabilities in terms of accuracy and access to reliable triage and screening tools, and thereby facilitate earlier detection of disease risk would result in improvements in the interruption of onward transmission, and subsequently disease prevention. Streamlining of drug development pipelines to aid rapid identification of novel compounds and effective treatment regimens would be invaluable in the face of rising rates of antibiotic resistance.

The initial applications of AI-based tools to these problems have produced exciting results but with an important caveat: their success has relied on access to large and comprehensive training and validation datasets. We consider this the principal issue currently hindering replication of the previous achievements of AI-based medicine in TB, being summarised in what we term a "data paucity cycle": a profound lack of data, particularly for validation purposes, leads to unsuccessful efforts to develop translatable tools, in turn resulting in a lack of evidence to convince further investment, ultimately leading back to data paucity.

Efforts from consortia, such as UNITE4TB, an innovative industry–academia collaborative network, stand to effect meaningful change [43]. With EUR 185 million funding for the acceleration of new treatment regimen

TABLE 1 Comparison of performance metrics from different physician and deep learning algorithm combinations in the diagnosis of acute respiratory failure due to three possible causes (pneumonia, heart failure or COPD)

Diagnostic framework	Absolute percentage difference in accuracy (95% CI)
Baseline (physician alone)#	
Physician+standard model	2.9 (0.5–5.2)
Physician+standard model+model-derived interpretation	4.4 (2.0–6.9)
Physician+biased (incorrect) model	−11.3 (−15.5– −7.2)
Physician+biased (incorrect) model+model-derived interpretation	−9.1 (−13.2– −4.9)

Diagnostic accuracy and percentage point differences in accuracy were determined by calculating predictive margins and contrasts across vignette settings after fitting a cross-classified generalised random effects model of diagnostic accuracy. #: diagnostic accuracy was 73.0% (95% CI 68.3–77.8%). Information from [42].

generation, key strategic decisions regarding expansive data generation, including detailed clinical, genomic and host transcriptomic data, across multiple international clinical treatment trials represent an unparalleled novel resource for the development of powerful AI models and a break in the data paucity cycle.

Achieving the WHO End-TB Strategy targets and a future without TB will require concerted efforts in developing novel strategies. AI-based technologies have produced impressive advances in diagnosing and treating several diseases, but are reliant on the availability of large, comprehensive and high-quality datasets. High-level stakeholders and funding bodies in TB control programmes can become key effectors of change through commitments to quality data generation and prioritising collaborative data-sharing cultures.

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