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Artificial neural network for pulmonary rifampicin resistant tuberculosis screening Indonesia : a study in accuracy and cost-effectiveness analysis of the model

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Artificial Neural Network for Pulmonary Rifampicin Resistant Tuberculosis Screening in Indonesia: A Study in Accuracy and Cost-effectiveness Analysis of the Model

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โครงข่ายประสาทเทียมสำหรับการตรวจคัดกรองวัณโรคปอดที่ดื้อยาไรแฟมพิซินในประเทศอินโดนีเซีย การศึกษาความแม่นยำและการวิเคราะห์ความคุ้มทุนของโมเดล

นายบูมิ เซาเฮริ เฮอร์แมน

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาสาธารณสุขศาสตรดุษฎีบัณฑิต
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บูมิ เซาเฮริ เฮอร์แมน : โครงข่ายประสาทเทียมสำหรับการตรวจคัดกรองวัณโรคปอดที่ดื้อยาไรแฟมพิซินในประเทศอินโดนีเซีย การศึกษาความแม่นยำและการวิเคราะห์ความคุ้มทุนของโมเดล. (Artificial Neural Network for Pulmonary Rifampicin Resistant Tuberculosis Screening in Indonesia: A Study in Accuracy and Cost-effectiveness Analysis of the Model) อ.ที่ปรึกษาหลัก : ศ. ดร.สถิรกร พงศ์พานิช

ความเป็นมา: การวินิจฉัยวัณโรคที่ดื้อยาไรแฟมพิซินในปอด (RR-TB) ด้วยวิธีการตรวจสอบความไวต่อยา (DST) มีค่าใช้จ่ายค่อนข้างสูงและใช้เวลานาน และวิธี GeneXpert ซึ่งเป็นการตรวจวินิจฉัยอย่างรวดเร็วก็ยังไม่มีให้บริการอย่างแพร่หลายในประเทศอินโดนีเซีย การศึกษานี้มีวัตถุประสงค์เพื่อพัฒนาและประเมินประสิทธิภาพ CUHAS-ROBUST ซึ่งเป็นปัญญาประดิษฐ์ (Artificial Intelligence) ที่ใช้ตรวจคัดกรองวัณโรคที่ดื้อยาไรแฟมพิซิน (RR-TB)

วิธีการวิจัย :การวิจัยนี้เป็นการศึกษาภาคตัดขวางในผู้ป่วยที่สงสัยว่ามีวัณโรคที่ดื้อยาไรแฟมพิซิน (RR-TB) ด้วยการเพาะเชื้อจากเสมหะบนอาหารไข่ด้วยวิธีที่เรียกว่า Lowenstein Jensen (วิธีมาตรฐาน) และนำผลของพารามิเตอร์ 19 ตัวจากข้อมูลทางคลินิก ห้องปฏิบัติการ และรังสีวิทยา ซึ่งได้มาจากเวชระเบียนในโรงพยาบาล คณะแพทยศาสตร์ มหาวิทยาลัยฮาสานุดดิน ประเทศอินโดนีเซีย ตั้งแต่เดือนมกราคม พ.ศ. 2558 ถึงเดือนธันวาคม พ.ศ. 2562 ทั้งนี้ได้ใช้โมเดลโครงข่ายประสาทเทียม (ANN) ซึ่งถูกสร้างขึ้นพร้อมกับโมเดลจำแนกอื่นๆ โดยโมเดลนี้ได้นำมาทดสอบกับผู้เข้าร่วมวิจัยซึ่งถูกคัดเลือกในช่วงเดือนมกราคมถึงเดือนตุลาคม พ.ศ. 2563 รวมถึงได้ถูกนำไปใช้ในแอปพลิเคชันที่เรียกว่า CUHAS-ROBUST (ดัชนีตรวจสอบ) พร้อมทั้งใช้ค่าความไว (Sensitivity) ความจำเพาะ (Specificity) และความแม่นยำ (Accuracy) มาการประเมินประสิทธิภาพของโมเดลนี้. การวิจัยเชิงคุณภาพด้วยวิธีการวิเคราะห์เนื้อหา (content analysis) ได้ดำเนินการในช่วงเดือนกันยายน 2563 ถึงเดือนตุลาคม 2563 โดยบุคลาการทางการแพทย์จากหน่วยบริการสาธารณสุขปฐมภูมิได้ถูกเชิญด้วยระบบออนไลน์เพื่อทดลองใช้แอปพลิเคชันและถูกสัมภาษณ์ผ่านวิดีโอคอล ได้มีการถอดคำสัมภาษณ์เพื่อใช้เป็นข้อมูล ทั้งนี้มีการใช้เทคนิคการวิเคราะห์แก่นสาระเชิงอุปนัยจากความอิ่มตัวที่เกิดขึ้นจากการเก็บข้อมูล ส่วนข้อมูลเชิงบรรยายของผู้เข้าร่วมวิจัย ประสบการณ์การใช้แอปพลิเคชั่น และผลที่คาดว่าจะเกิดขึ้นในบริการด้านสุขภาพได้ถูกนำรวบรวมสรุปไว้. การวิเคราะห์ต้นทุนประสิทธิผล (Cost effectiveness analysis) ของต้นทุนทางตรง (Direct cost) ได้จากข้อมูลของผู้เข้าร่วมวิจัย 330 คนที่ใช้วิธี Genexpert และโมเดล ซึ่งยืนยันด้วยวิธีการตรวจสอบความไวต่อยา (DST) จำนวนปีสุขภาวะ (QALYs) ในผู้ป่วยวัณโรคที่ไม่ได้รับการรักษาได้นำมาใช้เพื่อประมาณการผู้ป่วยวัณโรคที่ไม่ได้รับการวินิจฉัย (การเจ็บป่วยเฉียบพลัน การเจ็บป่วยเรื้อรัง และการเสียชีวิต) อัตราค่าต้นทุน-ประสิทธิผลส่วนเพิ่ม (ICER) ถูกนำมาคำนวณและสร้างเป็นกราฟ

ผลการวิจัย :ผู้เข้าร่วมวิจัยทั้งหมด 487 ราย (32 เชื้อดื้อยาหลายขนาน/ 57 เชื้อดื้อยาไรแฟมพิซิน, 398 ไม่ดื้อยา) ได้ถูกคัดเลือกเพื่อใช้ในการสร้างโมเดลและผู้เข้าร่วมวิจัย 157 คน (23 เชื้อดื้อยาหลายขนาน และ 21 เชื้อดื้อยาไรแฟมพิซิน) ในการทดสอบแบบไปข้างหน้า พบว่าโมเดลสมบูรณ์ของโครงข่ายประสาทเทียม ให้ความแม่นยำ 88% (95% CI 85-91) ความไว 84% (95% CI 76-89) และ 90% ความจำเพาะ (95% CI 86-93) โมเดลโครงข่ายประสาทเทียมนี้มีประสิทธิภาพเหนือกว่าโมเดลจำแนกอื่นๆ และได้ถูกนำไปใช้ในแอปพลิเคชัน CUHAS-ROBUST. ผู้เข้าร่วมทั้งหมด 33 คน (อายุเฉลี่ย 33.12 ปี) ได้ถูกคัดเลือกจากทุกภาคของประเทศอินโดนีเซีย ผลการวิจัยนี้แสดงให้เห็นว่า วัณโรคที่ดื้อยาไรแฟมพิซินเป็นภัยคุกคามใหม่ และการวินิจฉัยมีอุปสรรคที่สำคัญคือระยะเวลาที่ใช้ในการรอรับการรักษาและส่งผลให้ได้รับการรักษาที่ล่าช้าอย่างหลีกเลี่ยงไม่ได้ ถึงแม้จะมีการพยายามเอาชนะปัญหาการคัดกรองวัณโรคที่ดื้อยาไรแฟมพิซินด้วยการคาดการณ์ที่รวดเร็วประสิทธิภาพการคัดกรองและความน่าเชื่อถือของการเก็บรวบรวมข้อมูลสำหรับพารามิเตอร์ที่ใช้ในแอปพลิเคชัน CUHAS-ROBUST ยังคงเป็นสิ่งหลักที่ต้องพัฒนาต่อไป อย่างไรก็ตามแอปพลิเคชันนี้ช่วยเสริมความมั่นใจในการตัดสินใจ สนับสนุนการทำหัตถการทางการแพทย์ การเฝ้าระวัง และส่งเสริมการใช้วิธีการคัดกรองที่ต้นทุนต่ำ. ส่วนการวิเคราะห์ต้นทุนประสิทธิผล อัตราค่าต้นทุน-ประสิทธิผลส่วนเพิ่ม (ICER) ของการเสียชีวิตคือ -3601.706137 ส่วน ICER การเจ็บป่วยเฉียบพลันคือ -17225.55 และ ICER การเจ็บป่วยเรื้อรังคือ -825.391 ความไวขั้นต่ำของโมเดลที่จะไม่ผ่านความเต็มใจที่จะจ่าย (Willingness to pay) ที่จำนวนเงิน 100 ยูเอสดอลลาร์ ต่อ QALYs เท่ากับ 80.6% ในส่วนความชุกของโรคที่คาดหวังของวัณโรคที่ดื้อยาไรแฟมพิซินตามการคัดกรองโดยใช้โมเดลนี้ คือ 14.8% ถึง 23.3% ทั้งนี้ผลดังกล่าวนี้สอดคล้องกับค่าใช้จ่ายเฉลี่ย ซึ่งสะท้อนความโดดเด่นของโมเดลนี้

สรุป : แม้ผลจากโมเดลโครงข่ายประสาทเทียมในแอพพลิเคชั่น CUHAS-ROBUST จะมีความไวที่ต่ำกว่าผลลัพธ์ GeneXpert ทั่วโลก CUHAS-ROBUST ยังคงมีประสิทธิภาพดีกว่าโมเดลจำแนกอื่นๆ ของปัญญาประดิษฐ์ และได้มีการนำไปใช้จริงในแอปพลิเคชัน โดยบุคลากรทางการแพทย์สามารถใช้เครื่องมือดังกล่าวในการคัดกรองโรคโดยเฉพาะในหน่วยบริการปฐมภูมิ นอกจากนี้ การศึกษานี้ยังแสดงให้เห็นถึงบทบาทของปัญญาประดิษฐ์ ในการช่วยส่งเสริมคุณภาพการดูแลสุขภาพ และผลักดันความพยายามด้านสาธารณสุขในการต่อสู้กับวัณโรค ทั้งนี้ข้อได้เปรียบของอุปกรณ์นี้คือมีความคุ้มค่าแม้จะต้องการขยายการทดสอบให้เพิ่มมากขึ้น

สาขาวิชา	สาธารณสุขศาสตร์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2563	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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Bumi Zulheri Herman : Artificial Neural Network for Pulmonary Rifampicin Resistant Tuberculosis Screening in Indonesia: A Study in Accuracy and Cost-effectiveness Analysis of the Model. Advisor: Prof. SATHIRAKORN PONGPANICH

Background: Diagnosis of Pulmonary Rifampicin Resistant Tuberculosis (RR-TB) with the Drug-Susceptibility Test (DST) is costly and time-consuming, and the GeneXpert for rapid diagnosis is not widely available in Indonesia. This study aims to develop an Artificial Neural Network model and evaluate the deployed model performance for RR-TB screening.

Methods: A cross-sectional study involved suspected RR-TB patients with complete sputum Lowenstein Jensen DST (reference) and 19 clinical, laboratory, and radiology parameter results, retrieved from medical records in hospitals under the Faculty of Medicine, Hasanuddin University Indonesia, from January 2015-December 2019. The Artificial Neural Network (ANN) models were built along with other classifiers. The model was tested on participants recruited from January 2020-October 2020 and deployed into CUHAS-ROBUST (index test) application. Sensitivity, specificity, and accuracy were obtained for assessment. A qualitative approach with content analysis was performed from September 2020 to October 2020. Medical staff from the primary care center were invited online for application trials and in-depth video call interviews. Transcripts were derived as a data source. An inductive thematic data saturation technique was conducted. Descriptive data of participants, user experience, and impact on the health service was summarized. Cost-effectiveness analysis of direct cost was made using the data of 330 participants who underwent Genexpert and Model, confirmed by DST. The Quality Adjusted Life years of TB being untreated was used as the approximation of the undiagnosed TB (acute morbidity, chronic morbidity, and mortality). The Incremental Cost-Effectiveness Ratio (ICER) was calculated.

Results: A total of 487 participants (32 Multidrug-Resistant/MDR 57 RR-TB, 398 drug-sensitive) were recruited for model building and 157 participants (23 MDR and 21 RR) in prospective testing. The ANN full model yields 88% (95% CI 85-91) accuracy, 84% (95% CI 76-89) sensitivity, and 90% specificity (95% CI 86-93). This ANN model outperforms other classifiers and selected for the CUHAS-ROBUST application. A total of 33 participants (an average of 33.12 years old) were recruited from all parts of Indonesia. The findings show that DR-TB is a new threat, and its diagnosis faces obstacles particularly prolonged waiting time and inevitable delayed treatment. Despite overcoming the RR-TB screening problems with fast prediction, the dubious screening performance, and the reliability of data collection for input parameters were the main concerns of CUHAS-ROBUST. Nevertheless, this application increases confidence in decision making, promotes medical procedure compliance, active surveillance, and enhancing a low-cost screening approach. A cost-effectiveness analysis was made. The ICER Mortality value is -3601.706137. The ICER Acute Morbidity value is -17225.55 and The ICER Chronic Morbidity value is -825.391. The very minimum sensitivity of the model to not surpass the willingness to pay (WTP) of 100 USD per QALYs gained is 80.6%. The ideal prevalence of RR-TB according to the screening using model is 14.8% to 23.3%. Using the average cost, the results still consistent, showing the model as the dominant intervention

Conclusions: Despite showing lower sensitivity than global GeneXpert results. The ANN-CUHAS ROBUST outperforms other AI classifier models, and by deploying it into the application, the health staff can utilize the tool for screening purposes particularly at the primary care level. Moreover, this study demonstrates AI's roles in enhancing healthcare quality and boost public health efforts against tuberculosis. The advantage of this device is cost-effective although it should need a bigger test expansion.

Field of Study:	Public Health	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....

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I will give thanks to you, LORD, with all my heart; I will tell of all your wonderful deeds.

I would like to express my gratitude to my advisor, Prof. Sathirakorn Pongpanich, and committee member of my dissertation for all the supports and guidance during my study. To all lecturers and staff of The College of Public Health Science. To my family for the endless support. My colleagues at the University of Liverpool, Kanazawa University, Niigata University, and Centre Hospitalier Universitaire (CHU) Grenoble Alpes. To the team in Indonesia, particularly dr Agussalim Bukhari, dr Muhammad Dwi Wahyu and dr Muthiah Abustani. To the Ph.D. batch 61 for the awesome years. To my support system, Aye Chan Oo, Naw Wah Ka Paw, Aye Nyen Ei, and Htet Myat Aung, also Dian Ningrum and her husband. and the last, the Singaporean Diaspora and Indonesian students in Thailand.

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CHAPTER 1

INTRODUCTION

1. BACKGROUND

1.1 Epidemiology of Tuberculosis

Tuberculosis has now resurfaced and becomes a transmissible disease that requires a massive effort to eradicate. Mycobacterium tuberculosis, the disease's known causative agent, infects the lung as a primary target organ and spreads to other organs. The vast variety of diseases necessitates a large and time-consuming effort to diagnose and treat. Furthermore, the upward trend can be seen since as by default, mycobacterium spread through the air in air droplets and remain viable for a longer time. Moreover, a longer regiment of various drug combinations and serial follow-up complicates the efforts(1).

In its survey, Global Tuberculosis Report 2018, the World Health Organization (WHO) reported that tuberculosis mortality reached 2 million worldwide in 2017, with approximately 10.0 million people infected with tuberculosis. The vast majority of the group is made up of adults who live in Asia and Africa. Converting this statistic to an incidence rate yields 10 per 100,000 people in developed countries, and this figure increases to 500 in developing and low-income countries. Another form of dormant tuberculosis known as latent tuberculosis is found in approximately 25% of people worldwide (2).

Indonesia is regarded as a high-burden country that is battling tuberculosis eradication. This country had an estimated 842,000 cases of tuberculosis in 2017, but only 442,172 were recorded. Despite an annual drop in tuberculosis deaths over the last 17 years, 116,000 people have died as a result of the disease. One of the most important problems that Indonesia faces is a low number of people covered by treatment (only 53%). Furthermore, less than 90% of people undergoing (86%) completed treatment successfully, as expected by the End TB Strategy (3). The incidence rate of tuberculosis is approximately 254 cases per 100,000 people. Very far from the End TB program's goal of achieving a tuberculosis incidence rate of fewer than 85 cases per 100,000 population by 2020 (4)

Globalization, which affects health, specifically disease transmission, is what causes this disease to "re-emerge" and become more complicated. As humans can now move and migrate to another country more quickly, and

the borders of each country begin to "diminish," this affects tuberculosis transmission since this disease can now be found in high-income countries brought from high-burden countries. This condition is exacerbated by an unclear policy of tuberculosis screening in these countries, especially in a specific group such as migrants. By far, if this is not addressed, tuberculosis elimination will be ineffective. Well-managed prevention, screening, diagnosis, and treatment program should be put in place. However, the perfect scheme does not come cheap, putting a strain on the country's healthcare budget. To conclude, tuberculosis remains a global threat to public health, and there is a need for collaborative efforts to eradicate the disease (5)

1.2 Outcome of Tuberculosis Treatment

1.2.1 Definition of Outcomes

The current guidance elaborates on the tuberculosis treatment outcomes of cure, failure, relapse, resistance, and death. Cases can be cured by prescribing the standard regiment, and therefore disease spread from sick people can be avoided. A serial follow-up test and standardized diagnostic technique are used to assess these outcomes. Different care results necessitate wider management efforts. (6)

1.2.2 Unfavorable Outcomes in Specific Groups

People with immune system defects are more likely to become ill, have adverse results, and spread diseases to other non-susceptible groups. A particular population, such as HIV-infected people, has significantly negative outcomes due to changes in immune systems that limit the body's ability to remove tuberculosis. Some research was conducted to find the best approach for the management of this population, which included the inclusion of an antiretroviral regimen in addition to tuberculosis management. HIV testing is also conducted on those that are TB infected, and vice versa. This is known as bi-directional screening. (7)

As there is a possible reason why an immunocompromised body has a bad outcome, many doctors and researchers are now looking into another disease that may decrease the efficacy of the immune system, delaying clinical improvement and rendering the pathogen resistant. People with diabetes mellitus have been identified as a population at risk of poor tuberculosis outcomes, as several studies have shown that an uncontrolled glycemic profile is associated with immune dysfunction (8). Additionally, the most recent protocol for managing this case has not been

well established or is being undervalued, including tuberculosis screening in this population. The problem is that these people have no awareness of whether they can spread the disease, and the pathogen has a chance to evolve a mechanism to adapt to the weak immune system, leading to an increase in drug-resistant cases in this population. The presumption is that these diabetics, as well as people with chronic illnesses, have a latent infection. Mycobacterium tuberculosis inhaled into the body may not be completely eliminated, remaining viable and entering the dormant period, due to prolonged dysfunction of the system organ compounded by altered immunity. As the immune system deteriorates with age and the disease progresses to a more advanced stage (for example, uncontrolled blood glucose or impairment of lung function in a patient with Chronic Obstructive Pulmonary Disease), those inhaled-dormant agents that survive the initial removal by the weakened immune system have a chance to activate and adapt (including mutation of several genes). This is how latent tuberculosis, especially in these populations, can result in a global burden, as estimated in recent studies, including delayed cure and the risk of developing drug-resistant cases. (9) To address these issues, diagnostic methods have been developed (interferon-gamma assay or simple tuberculin test/TST). Despite the reliable performance, these are not ideal for use in a low-resource environment due to human resource limitations and the accessibility of the unit itself (10).

Some groups with unsafe behavior, such as those who smoke, consume alcohol, use drugs, and maintain an unhealthy lifestyle, as well as those with particular demographic features (such as elderly people, people without health insurance, and men), are those who have an undesirable outcome from tuberculosis, such as drug resistance. This is aggravated by environmental factors such as living in an overcrowded house with inadequate ventilation or working as a caregiver with frequent contact with a tuberculosis patient (11).

In summary, these groups could be at an elevated risk of transmitting the disease to healthy individuals, experiencing delayed clinical development, and potentially increasing the chance of developing drug-resistant tuberculosis cases. As a result, appropriate screening and management protocols should be developed and implemented in an acceptable yet efficient manner.

1.3 The drug-resistant, epidemiology, and burden

Tuberculosis elimination has been highlighted in the Sustainable Development Goals (SDGs), and a series of guidelines are adopted internationally to comply with the End TB strategy 2016-2035. By doing so, the global burden of tuberculosis can be minimized and lowered by the end of 2035. According to this program's findings, 3.9 percent of new cases and 21 percent of previously treated cases were diagnosed as rifampicin-resistant (RR) or multidrug-resistant in 2015. (MDR). Furthermore, the reliability of this data can be called into question, as incomplete data is normal in high-incidence countries. According to global figures, approximately 58.6% of the estimated cases of RR/MDR were announced in 2015. And as few as 36.7 percent will be able to receive adequate care (12).

Tuberculosis with Rifampicin Resistance and Multi-Drug Resistance Tuberculosis cannot be separated. Rifampicin and isoniazid resistance is a component of Multi-Drug-resistant, meaning that Multi-Drug-resistant is also a subset of rifampicin-resistant. Since the vast majority of tuberculosis cases are pulmonary tuberculosis, which is the form that spreads the disease most rapidly, the objective is primarily on eliminating this type of tuberculosis. More precise research using the mathematical model was implemented in India, the Philippines, Russia, and South Africa, suggesting that the incidence of MDR reached 325 percent (270-358), with Russia contributing 124 percent (94-162) and India attributing 89% (45-817). In 2040, the Philippines and South Africa are projected to have 57 percent (30-76) of the population. Another advanced term for drug-resistant tuberculosis is Extensive Drug-resistant (XDR) tuberculosis, which is forecasted to be 8.5%-90% in 2040. This is by far the most critical point to accentuate: the threat of tuberculosis is not about new infections, but about the growth of resistant cases over the next two decades. (13)

What is the exact pressure that drug-resistant tuberculosis imposes? Transmission of tuberculosis with a drug-resistant strain to a person, especially a person who has never had tuberculosis previously (referred to as primary drug-resistant tuberculosis). One of the most vulnerable categories is the caregiver who has frequent contact with the drug-resistant patient (14). The rise in patient numbers caused by drug-resistant tuberculosis is exacerbated further by the difficulty of the drug treatment itself, which makes it expensive to treat and has a wider economic impact. A study examining the economic burden of multidrug-resistant tuberculosis in Indonesia, Kazakhstan, and

Ethiopia revealed that the cost of tuberculosis care is escalating, specifically for drug-resistant tuberculosis. The effect is not limited to the health provider; these patients are often stigmatized and isolated, which results in unemployment, income loss, and career loss, further worsening their financial status, as well as the loss of active age workers. (15)

On the provider's hand, the burden of drug-resistant tuberculosis is in the diagnosis and treatment processes. The new technology provides a method for assessing the causative agent and detecting drug resistance at the molecular level. A diagnostic approach based on direct observation of mycobacterium development, metabolic activity, and substance (such as the NAAT test from GeneXpert) and genotyping identification of the gene (rpoB and katG) has been implemented in the clinical environment, but not all tests can be undertaken due to cost and repetitive follow-up procedures. (16)

At the country level, only six of the thirty countries studied were able to include universal access to multidrug-resistant tuberculosis care in 2015, while the remaining countries struggled to ensure the availability of diagnostic methods and treatment (17). Additionally, the treatment of drug-resistant tuberculosis differs between individuals depending on the findings of a drug susceptibility test, indicating that no two individuals receive the same treatment. Then again, the efficacy was poorly understood. (18)

In summary, the adverse outcome of tuberculosis, especially drug-resistant tuberculosis, is a significant concern, and while specific groups at risk have been recognized, the screening protocol, diagnostic management, and care for this condition are far from being optimal.

1.4 Diagnostic Modalities

One of the critical issues is how tuberculosis screening and diagnosis, especially for drug resistance, should be performed. The issues found are that conventional techniques, despite their increased reliability, are not readily accessible and, even though they are, a significant amount of revenue should be allocated. In Indonesia, the number of diagnostic modalities for drug-resistant tuberculosis seems far from optimal. Indonesia has only 7326 accredited sputum smear analysis laboratories, accompanied by 963 rapid molecular diagnostic testings (GeneXpert) centers since 2012, 21 culture laboratories, and 11 globally certified drug sensitivity testing laboratories to accommodate a nation of 265 million (19). These modalities depend on sputum as a source of the sample, but other

body parts or body fluids are permissible. This hypothesis is based on a plausible mechanism for tuberculosis transmission through the respiratory tract. As a result, the emphasis of drug-resistant removal is primarily on the pulmonary type. Finally, there is a need to resolve the problem of the restricted number of modalities.

1.5 Artificial Intelligence.

Artificial intelligence is described as a tool that assists humans in their daily lives. The machine performs this function by executing basic tasks (such as object recognition, choice in a search engine, or even promoting driverless vehicle technology), which is referred to as supervised learning, when further complicated tasks such as decision-making and problem-solving, which is referred to as unsupervised learning, are developed. Through introducing artificial intelligence, major and radical improvements in human life can be accomplished, including the eradication of social and economic issues such as poverty (20)

1.6 Artificial Intelligence and Medicine

In clinical practice, accuracy is needed for disease diagnosis, and the issue that arises is interobserver reliability. A neurologist may diagnose hemorrhagic stroke based on signs and symptoms alone, while a general practitioner requires further confirmatory testing. As a result, there are several algorithms and strategies for diagnosing a disease. This is focused on a pattern of signs and symptoms associated with such illnesses, such as rebound tenderness and right lower quadrant abdominal pain, all of which suggest appendicitis. Risk scoring is a basic algorithm that is used in conjunction with "machine learning" to alleviate the burden in decision-making. The Alvarado score is one of the most frequently used risk-scoring algorithms for appendicitis diagnosis. It includes multiple signs and symptoms associated with appendicitis in each scoring. This risk score was developed using advanced statistical techniques such as LOESS (Locally Estimated Scatterplot Smoothing) (21)

The age of the supercomputer, aided by the availability of big data (as health care providers now engaged in electronic health records), allows for the possibility of improving the accuracy of an algorithm for detecting disease. The artificial neural network, a method for deep learning that resembles human neuron cells, has become popular. This network can be used to predict continuous data or act as classifiers, which helps measure the possibility of a disease occurring. In the medical sector, an example of an Artificial Neural Network is the dengue's neural network

built during a study in Mexico and Puerto Rico. This model is constructed using a variety of available data and makes accurate predictions(22) through compiling all available data on potential predictors.

How is this intricate structure incorporated into the lives of people? There are several simple ways to "translate" this model. The Application Programming Interface (API) is a technique for developing a basic application that can run on any device, including a mobile phone. Via a series of procedures and code translation, the artificial intelligence model can be translated into an easy-to-use application. Eventually, anyone who has access to this application would benefit, particularly in low-resource settings where drug-resistant assessment is likely to occur.

2. RESEARCH GAP

As a consequence of the preceding clarification, study gaps can be identified:

• Tuberculosis is a major public health problem worldwide and in Indonesia, with a growing trend of drug-resistant cases.

• Rifampicin resistance is associated with MDR tuberculosis.

• A distinct group of tuberculosis patients has been identified, along with their predisposing factors for drug-resistant tuberculosis.

• Indonesia's health infrastructure is insufficient to deal with drug-resistant cases, worsened by costly diagnosis and treatment.

• Electronic records in healthcare providers are a reliable source for big data analysis.

• Artificial Intelligence (for example using the Artificial Neural Network) can be used to generate a predictive model based on the information provided by predictors.

• The predictive model generated by Artificial Intelligence can be a promising tool for rifampicin-resistant screening, especially in pulmonary tuberculosis patients and in a low-resource setting in Indonesia.

3. RESEARCH OBJECTIVES

The research will be performed with the following objectives based on the current state of the interest problem:

• To build an Artificial Intelligence Model based on an Artificial Neural Network **to screen** for Pulmonary Rifampicin-Resistant Tuberculosis.

• To evaluate the model's performance and validity **concerning** the gold standard (drug susceptibility test).

• To incorporate the optimal model into an application so that the end-user (TB manager) can make use of the tools.

• To evaluate the screening performance of the deployed model against GeneXpert using actual prospective data and to conduct a cost-effectiveness study using culture as the gold standard.

4. RESEARCH QUESTIONS

The research questions are derived from the following research objectives:

• Which Artificial Neural Network structure is appropriate for screening Pulmonary Rifampicin Resistant Tuberculosis?

• How accurate and reliable are the results generated by the Artificial Neural Network model concerning the gold standard (drug susceptibility test)?

• How does an Artificial Neural Network Architecture become embedded in a model and application?

• How effective and efficient is the deployed model in comparison to the current GeneXpert System tested by a real data setting?

5. HYPOTHESIS

The hypothesis is based on the second research questions and comparison to a gold standard of diagnosis which :

- Null Hypothesis: The Artificial Neural Network model demonstrates equivalence in screening for Pulmonary Rifampicin Resistant Tuberculosis as compared to gene Xpert, confirmed by the gold standard (drug susceptibility test) in real setting data

- Alternative Hypothesis: The Artificial Neural Network model provides non-equivalence results of screening Pulmonary Rifampicin Resistant Tuberculosis in comparison with gene Xpert, confirmed by the gold standard (drug susceptibility test) in real setting data.

6. FUTURE BENEFIT

The artificial neural network model, when built into a model input for implementation, will be an effective screening tool for Pulmonary Rifampicin Resistant Tuberculosis, particularly in low-resource settings with remote health care services.

7. CONCEPTUAL FRAMEWORK AND STUDY FRAMEWORK

Figure 1.1 Conceptual Framework of Variables

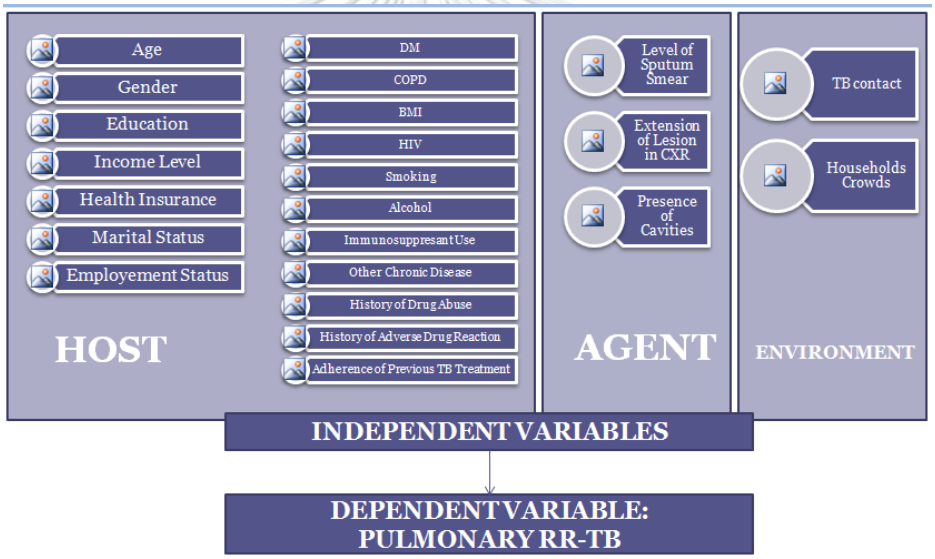
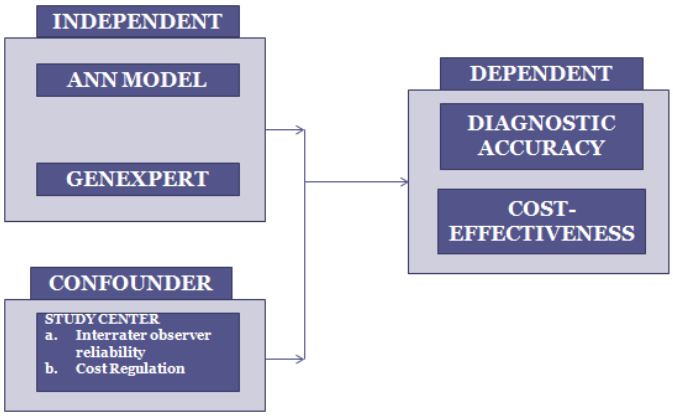


Figure 1.2.Study Framework.



The conceptual framework is the principle underlying the relationships between parameters and their corresponding outcomes for the first three objectives. The framework of the study serves as the conceptualization of the fourth objective.

8. OPERATIONAL DEFINITION

This is the accepted description and terminology for the words described and defined in this proposal:

• Rifampicin-Resistant Tuberculosis of the Pulmonary: All cases coded as A.15 and A.16 with at least U.50.0; U50.2-4

• Drug-Susceptibility Test: A test used to assess a drug's ability to prevent the growth of microorganisms in culture.

• Rapid Molecular Test: The GeneXpert is a cartridge-based nucleic acid amplification test (NAAT) designed to perform rapid tuberculosis diagnosis and antibiotic sensitivity testing simultaneously.

• Artificial Neural Network: An Artificial Neural Network is a collection of interconnected processing elements that are linked by weighted connections. The training algorithm changes the relation weights iteratively to minimize error.

Factors of Sociodemography

a. Age is classified as the participants' age (in years) at the time of admission to the study center for drug-resistant evaluation.

b. The word "sex" refers to the gender assigned at birth.

c. The educational attainment standard will be determined following the national educational framework.

d. Health Insurance is described as the possession of both national and private health insurance to cover medical expenses.

e. Marital Status is listed as either single (not married, divorced, or widowed) or married.

f. Employment status is characterized as having a job that provides for basic needs.

g. Income is the monthly wage or earnings.

Disease and Health Behavioural History

a. Diabetes Mellitus is diagnosed by a physician as E.11 in ICD 10

b. Chronic Obstructive Pulmonary Disease is diagnosed as J.44 in ICD 10.

c. Body Mass Index (BMI) is defined as the ratio of one's body weight in kilograms to one's height in meters squared.

d. In ICD 10, Human Immunodeficiency Virus is classified as B.20.

e. Smoking is characterized by the Index Brinkman, which indicates the history and severity of a smoking habit.

f. Alcohol consumption is characterized as recent alcohol consumption within the last one year or prior to tuberculosis treatment.

g. Immunosuppressive agents are described as the use of immunosuppressive agents, including glucocorticoids, for an extended period (greater than three weeks) or the use of immunosuppressive agents for a brief period to treat cancer.

h. A History of Drug Abuse is described as any history of injectable morphine use or substance abuse such as alcohol, amphetamine, or an illegal substance.

i. A history of an adverse tuberculosis drug reaction, defined as an adverse reaction occurring immediately or later after taking tuberculosis medication.

j. Adherence to previous tuberculosis treatment, defined as the administration of all prescribed medications in the prescribed dosage and time frame.

k. Existence of Chronic Disease involves the presence of any other chronic disease, such as stroke, heart disease, mental illness, or any other disease requiring long-term management and therapy.

Agent's Manifestation

a. Sputum Smear Level is defined as the number of acid-fast bacilli detected under microscopic inspection

b. Lesion Extension in Radiology Examination is defined as the number of lung zones with a distinctive appearance consistent with tuberculosis.

c. Cavities described as any cavity visible on a radiographic image of the lung

Factors in the Environment

a. Previous contact with tuberculosis patients, identified as any contact with tuberculosis positive cases

CHAPTER 2

LITERATURE REVIEW

1. TUBERCULOSIS

1.1 Infection Initiation

Mycobacterium tuberculosis is the bacterium that causes tuberculosis. Transmission occurs when viable mycobacterium from inhaled air droplets passes to the distal portion of the respiratory tract, called the alveolus. This activates the first immune reaction, phagocytosis, the engulfment of bacteria by alveolar macrophages. Phagocytosis may be unable to kill the engulfed mycobacterium in some circumstances. Subsequently, a certain amount of mycobacterium multiply and spread through the blood (hematogenous) and lymphatic vessels, infecting another organ, and causing a variant of tuberculosis known as extrapulmonary tuberculosis. The primary infection site promotes the formation of granuloma, which traps the mycobacterium within a low-oxygen, encapsulated tissue, suppressing bacteria growth. If the body effectively eradicates all circulated bacteria, tuberculosis becomes dormant or inactive and is referred to as latent tuberculosis. Despite the immune system's complexity, once the immune system is altered, the viable organism inside the granuloma may reactivate. Individuals who are immunocompromised often develop tuberculosis, even though their history of interaction with active tuberculosis patients is uncertain, implying that latent tuberculosis is the cause of the active disease (23).

How Mycobacterium tuberculosis permeates the human body is determined by its unique body structure, which exhibits a variety of virulence profiles. The most crucial part is the cell membrane, which is made of a sturdy lipid structure composed of mycolic acid and lipoarabinomannan. Mycobacterium can be identified by the immune system by the binding of these structures to the immune cell. As previously stated, recognized mycobacteria are engulfed into the cytoplasm of an immune cell for chemical destruction, but some findings indicate that Mycobacterium tuberculosis can evade this process by prohibiting the phagosome and vacuole that contain the bacteria from forming a joint, thus affecting the release of the oxidative and nitrosative substances that can destroy it. Due to the mycobacterium's successful adaptation to the immune cell's inner system, this is an excellent opportunity for the mycobacterium to remain dormant and begin replication at a later stage (24).

1.2 Immune response in tuberculosis

It is critical to understand how the immune system responds to the mycobacterium because several factors contribute to the immune system being altered, both modifiable and unmodifiable. Innate immunity is vital for tuberculosis eradication. Innate Immunity is dependent on the activation of a variety of leukocytes, including the Natural Killer (NK) cell and macrophage cells, most notably the alveolar macrophage. The addition of mycobacterium's pathogenic components to the cell initiates the identification process and the mobilization of some necessary defense mechanism cells. One of the most straightforward processes is to induce apoptosis or the death of infected cells. To optimize the process, adaptive immunity produces unique antimicrobial substances that allow the macrophage to recognize and engulf the mycobacterium more easily. The lymphocyte B cell and T cell are the primary cells involved in these functions, notably in the release of pro- and anti-inflammatory cytokines and specific ligands. Conditions or causes that can impair this cascading mechanism include the involvement of HIV, which hinders lymphocyte function, diabetes, which disrupts phagocytosis function, and any other chronic disease or aging (25).

The respiratory tract has been identified as the primary site of infection, as the mycobacterium enters the body through inhaled air droplets. The distal respiratory tract cells, especially the airway epithelial cells, will then conduct a first-line defense mechanism (Alveolar Epithelial Cell). This cell produces many protective compounds, including surfactant liquid and ligand expression. The surfactant layer will keep the mycobacterium from coming into contact with the tissue underneath. The innate immune system can destroy floating foreign bodies and mycobacterium. The second phase includes the involvement of specific ligands known as Toll-like receptors (TLR). This ligand is covalently bound to the lipoarabinomannan structure present in the cell wall of the mycobacterium. Mycobacterium bound with this ligand will be readily recognized by innate immunity cells, thus speeding phagocytic activity. This mechanism may be disrupted by the dissolution of the alveolar lineage and its main cells. This can be seen in smokers or in people who have structural changes in their lungs, such as those who have COPD (26).

A macrophage is referred to as the "eater" because it is capable of phagocytosis. After being ingested by the mycobacterium, this pathogen is entrapped within a vacuole. Via a particular process, a vacuole contains a material that kills bacteria. As bacteria are merged into the vacuole, the destructive substance interacts with

mycobacterium, resulting in the pathogen's death. Cathelicidin is a vital factor. This substance is activated by the expression of Toll-Like Receptors, and activation of the cAMP gene results in the formation of cathelicidin LL-37, which is recognized as a significant substance in altering the mycobacterium's lipid-membrane. Phagocytosis function may be interrupted in people with uncontrolled diabetes mellitus for an extended time (27)

Nitrite oxide is another important substance for killing mycobacterium intracellularly, especially within the macrophage cell. By transforming L-Arginine to N-OH-L-Arginine, the inducible enzyme Nitric Oxide Synthetases is triggered to create Nitrite Oxide (28). The nitrite oxide formed in this process is then dispersed into mycobacterium-containing phagosomes. (29)

Not only macrophages but also less protective cells such as lung epithelial cells, participate in this phagocytic action. Because this cell lacks a more powerful intracellular killing mechanism, the immune system will destroy the bacteria by triggering a cell-killing mechanism known as apoptosis; otherwise, the mycobacterium will survive long term and live to the next stage. This process is carried out by the CD8+ T cell, which induces the synthesis and production of cytokines such as interferon-gamma, which mediates the apoptosis of infected cells. (30)

The extracellular killing also happens in surfactant layers as a result of the hydrolase enzyme. This substance is formed in the alveolus by type II epithelial cells. Through carrying out hydrolase action, the pathogen's cell wall can be altered before reaching the next protection layer (31)

1.3 Standard Diagnosis

Tuberculosis is categorized clinically into two types: pulmonary and extrapulmonary tuberculosis (which accounted for a smaller percentage). Since the manifestations vary according to the target organ, different treatment modalities have been established to diagnose the case, but they are still mostly focused on signs, symptoms, and other distinctive features. The accessible standard for diagnosis is acid-fast staining, which is available in low-resource settings before sophisticated tech such as tuberculin skin testing, chest radiography, and molecular assessment (IgRA, GeneXpert MTB/RIF, Lipoarabinomannan Assay, and genotyping) becomes available. Culture continues to be the gold standard, as long as it is done accordingly (32).

1.3.1 Acid-fast staining

Sputum smears are the standard test for tuberculosis in the lungs. As per the theory, the mycobacterium is found in the air droplet during coughing or expectoration, which is the most common mode of disease transmission. Collecting sputum allows for direct examination and detection of the agent for diagnosis. The Ziehl-Neelsen and Kinyoun methods are the existing methods for this smear. The mycobacterium's cell wall is composed of a lipid layer that contributes to its infectivity. The technique for staining this cell wall is created by coloring the wall with a combination of phenol and fuchsin. Phenol may bind the mycolic acid compound to the wall and fuchsin strengthens the connection, leaving a bright red color that cannot be diluted with an acid alcohol rinse. The sputum is then colored with the counterstain dye, a blue pigment derived from methylene blue. The Ziehl Neelsen technique is distinguished from the Kinyoun method by the heating of the sputum smear, which is not done in the Kinyoun method. Although fuchsin acts as a chemical mordant, the addition of heat will act as a physical mordant which increasing the carbol's affinity for the lipid wall (33)

Tuberculosis diagnosis involves a minimum of two samples, one of which should be expectorated in the early morning (34). Without contamination of water, food, or other intakes, these morning samples improve the sensitivity of the test (35) (36), and as suggested in the International Standard of Tuberculosis for program reporting and therapy assessment (37) the Bacillary Index has been standardized to grade the degree of microscopic appearance, ranging from negative, scanty, 1+, 2+ and 3+ (38).

1.3.2 Radiology

Chest radiography has grown into a valuable diagnostic tool in tuberculosis. The alterations in the respiratory tract are a consequence of the body's attempt to remove mycobacterium. The Tumor Necrosis Factor/TNF alpha and the Matrix Metalloproteinase enzyme are two cytokines that play critical roles in the development of granuloma, cavitation, and fibrosis, respectively (39). The severe disturbance at the cellular level results in a change in airflow distribution, which is denoted by the words tuberculosis-COPD or Post-Tuberculosis Obstructive Syndrome (40). This suggests that the more radiologic manifestations observed in chest radiography, the more cellular resources have been expended on tuberculosis elimination. This means that a patient with a broader lesion has a "stronger" strain of mycobacterium which needs a bigger immune response to eliminate. Additionally, shortness of

breath caused by anatomical changes will ultimately worsen one's quality of life (41). Intriguingly, tuberculosis patients may present with certain atypical or nonspecific chest radiographic attributes that mimic those of another respiratory infection. Diabetes patients often have significant consolidation that does not include the upper lung region, which is typical of tuberculosis. This may impede diagnosis, since chest radiography may indicate some form of pneumonia rather than tuberculosis, and the extent of the lesion is not dependent on the duration of diabetes (42). Another presentation, miliary tuberculosis (tuberculosis with paddy grains consolidation in chest radiography), is unique from the others and is more likely to occur in children or HIV-positive individuals (43).

Chest X-rays and CT scans are the radiologic examinations of choice for pulmonary tuberculosis. Chest X-rays can reveal the pathologic appearance and are typically performed when clinical signs and symptoms suggest pulmonary tuberculosis but the sputum smear results are questionable. While CT scans are not routinely performed, they can provide improved imaging of the mediastinum lymphadenopathy, fungus consolidation, or identify cavities, which can aid in defining tuberculosis from other infections such as pneumonia. Ultrasound can detect any other non-specific characteristic, such as pleural effusion. While MRI can detect caseation (necrosis liquefaction) more effectively than a CT scan, it is not routinely performed and has a lower sensitivity (44). In radiology, pulmonary tuberculosis is classified into active and cured tuberculosis based on its appearance on X-Ray and CT. The term "active case" refers to a situation in which the disease is still progressing and clinical symptoms are still manifesting. In an active case, the upper zone of the lung will typically exhibit consolidation or a cavity with a thick-walled cavity. Miliary nodules are thin, around the size of a rice grain, and distributed to all zones of the lung, as seen in children and patients with tuberculosis and HIV. In children, an additional feature is an enlargement of the mediastinal lymph nodes. When the patient has recovered or there is no evidence of active infection, this stage is referred to as the cured type. Along with consolidation, the cavity wall will appear thinner or vanish entirely. A fibrotic line can be seen separating an enlarged distal airway closely mimics bronchiectasis from the distal airway structure(44).

1.3.3 Bacterial Culture

The World Health Organization (WHO) considers bacterial culture to be the gold standard for tuberculosis diagnosis. This is focused on the premise that the presence of any microorganism in a culture set up for

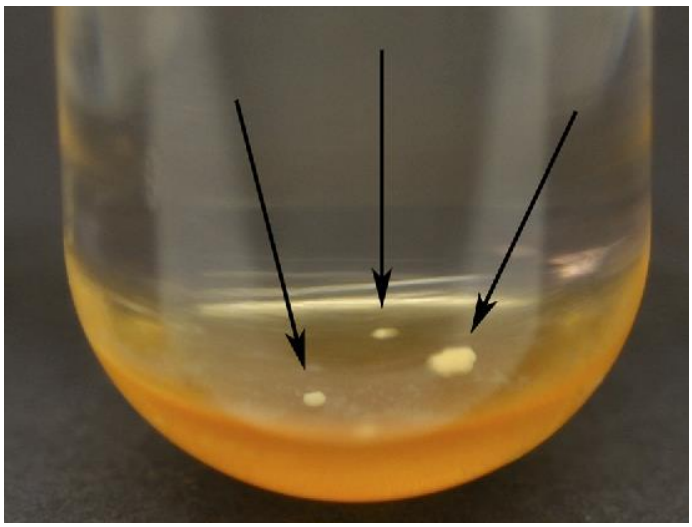
mycobacterium growth means that the sample positively contains tuberculosis bacterium. This procedure is also used to determine tuberculosis's drug sensitivity. The majority of samples for this test come from the respiratory tract (sputum, nasopharyngeal aspirates, or bronchoalveolar lavage)(45).

The Lowenstein Jensen Medium is the accepted standard for Mycobacterium tuberculosis and other Mycobacterium species culture. It contains malachite grey, glycerol, aspargine, coagulated eggs, the mineral salt solution containing potassium dihydrogen phosphate, magnesium sulfate, and sodium citrate, and also potato starch. It also includes antibiotics that inhibit both gram-positive and gram-negative bacteria. It is essential to confirm the colony to classify the bacteria. Growth can be tracked from 5 days to 8 weeks after bacterial culture (46).

Figure 2.1 A growth of Mycobacterium tuberculosis on a Lowenstein Jensen media, Shows a yellowish colony

Another culture that can be used is the Middlebrook 7H9 culture, which comprises ammonium sulfate, L-glutamic acid, sodium citrate, pyridoxine, biotin, disodium phosphate, monopotassium phosphate, ferric ammonium citrate, magnesium sulfate, calcium chloride, zinc sulfate, and copper sulfate. Additional compounds such as glycerol, oleic acid, albumin, and dextrose may be added to the culture. The mycobacteria growth indicator tube (MGIT) evaluates growth in this broth by inserting a fluorescent agent that is responsive to dissolved oxygen. Since mycobacterium absorbs oxygen, the basic measurement of this tube is fluorescence detection. This can expedite the diagnostic process, as even a slight change in metabolic processes indicates the existence of mycobacterium. (47).

Figure 2.2 A growth of Mycobacterium in Liquid medium



Several studies are conducted to evaluate the Lowenstein Jensen (48) and MGIT (Mycobacterium Indicator Growth Tube). According to a review, MGIT reproduces faster and at a higher rate than LJ alone, and both combinations outperform the standalone technique despite its negligible performance.(49).

Despite the reliability of the findings, this analysis is likely difficult to undertake in a low-resource environment. Subsequently, this diagnostic approach is expensive, and some occasions of contamination or improper specimen collection may impact the result (45).

1.3.4 Molecular Testing and Genotyping

The WHO has now approved the use of rapid diagnostic tests focused on the polymerase chain reaction (PCR) for presumed drug-resistant infections. Since 2012, Indonesia has used the Rapid Molecular Diagnostic test to improve the detection of drug-resistant tuberculosis. GeneXpert is a rapid diagnostic test focused on nucleic acid amplification that is used to identify mutations in genes located within the 81-bp core region of the bacterial RNA polymerase rpoB genome. This gene mutation is more noticeable than any other gene mutation, like katG and inhA. The Xpert employed a molecular beacon to specifically target the 81-bp core area. The bright fluorescence indicates that this molecular beacon has hybridized with the amplified DNA target. Clinical samples are kept at room temperature with reagents containing sodium hydroxide and isopropanol of a specific composition. This mixture is

then inserted into a cartridge, and the automated process begins. A positive finding is described as the presence of a positive signal in at least two of the five probes. The resistance is determined by comparing the test's period threshold. The gap of more than 3,5 cycles suggests that the patient is insensitive to rifampicin. The nonrespiratory sample exhibits similar sensitivity and specificity to the respiratory source but does not outperform it (50).

In Uganda, a sensitivity and specificity test on tuberculosis detection was conducted for Xpert MTB/RIF. Salivary sputum has greater sensitivity (66%) than other infected samples (blood-stained, purulent, or mucoid sputum) and an average sensitivity of 53%. Overall, the greater specificity (96%) means that the Xpert MTB/RIF could be used to rule out tuberculosis (51). Nevertheless, in a resource-constrained setting where geographical constraints are a major consideration, research in Nepal found that Xpert has a sensitivity of 85,4 percent in patients with positive sputum smears and 81 percent in those with negative sputum smears (52). GeneXpert outperforms liquid culture in identifying mycobacterium from salivary sputum, and interestingly, patients who have previously received treatment are more likely to have a negative culture test (53). Furthermore, the ability of Xpert in detecting rifampicin shows higher pooled sensitivity of 94% (95% CI 87%-97%) and pooled specificity 98% (95% CI 97%-99%) as shown by meta-analysis. By means, the gene Xpert can provide reliable results within a short time (54).

In terms of performance, a study conducted in Indonesia found that after implementing Xpert, there was a 15% increase in the detection of positive tuberculosis cases compared to the year before implementation. On the other hand, rifampicin resistance is 23% lower than it was before the introduction. However, this implementation accelerates the initiation of second-line therapy and reduces diagnostic wait (55).

Tuberculosis genotyping can be used to differentiate reactivation stage and recently transmitted disease. The genotype is often used to classify mycobacterium isolates in a culture. Genotyping in Mycobacterium is based on genetic polymorphism. Several frequently detected genes include the following: (katG, gyrB, gyrA, rpoB, hsp65, and sodA). A Polymerase Chain Reaction is used in the most recent genotyping protocol (PCR). Genotyping may be used for phylogenetic analysis to ascertain the mycobacterium lineage's origin (56). Certain mutations in the gene, such as rpoB for rifampicin resistance and katG for isoniazid resistance, may be associated with drug resistance (28). Genotyping, on the other hand, is often used in molecular epidemiology, but not for routine detection.

1.3.5 Other Methods

Tuberculin skin testing is based on a delayed hypersensitivity reaction in which tuberculin is administered intradermally on the volar surface of the forearm and examined 48–72 hours later. Tuberculosis infection is described by a cut-off of 10 mm, despite the possibility of confounding factors such as nontuberculous mycobacteria (NTM) infection or BCG vaccination. The lower cut-off is used for immunocompromised patients because the predicted hypersensitivity reaction was not detected in this population. (45).

Cytokine-based examinations are conceivable. This approach quantifies the Interferon Gamma Release Assay expressed by T-lymphocytes (QFT) and the number of IFN-secreting lymphocytes (45). The tests outlined above are primarily used to detect latent tuberculosis infection.

1.4 Treatment

1.4.1 Standard Regiment

Recently diagnosed tuberculosis of the lungs is managed with a standardized regimen that is adjusted according to the patient's condition, including body weight, liver function, and kidney function. Tuberculosis treatment stages range from two phases (the intensive phase and a continuation phase) lasting 6-9 months for new tuberculosis patients to three phases lasting 18-24 months for drug-resistant tuberculosis patients. The phases are determined by the intended use of the medication, with the initial phase emphasizing both bactericidal and bacteriostatic action and the continuation phase emphasizing sterilizing impact. Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide are the first-line antituberculosis medications that are often used during the uncomplicated stage. There are a few additional medications (second-line) available for difficult cases, as well as customized regimens for those with resistant cases. This change is made based on physician consideration about the clinical manifestation (57).

1.4.2 Rifampicin

Rifampicin exerts its antituberculosis activity by interfering with the DNA-dependent RNA polymerase (RNAP) in bacteria, resulting in a bactericidal and bacteriostatic impact. As a consequence, this inhibition affects bacterial replication. Rifampicin has a high rate of dissemination and penetration into tissue cells (58). The liver is responsible for rifampicin metabolism, and the drug's final product is excreted by the kidney in urine.

Consideration should be given to the assessment of liver function, as Rifampicin can affect the cytochrome P450 (CYP) 3A4 enzyme and thus disrupt the metabolism of any substance involving the CYP2C-enzyme in the liver. Additionally, since rifampicin binds with the hepatic P glycoprotein, it will affect all compounds that depend on or are transported by this protein, including warfarin, sulfonylurea, oral midazolam, triazolam, simvastatin, verapamil, and dihydropyridine calcium channel antagonists. Antifungal and antimicrobial medications metabolized by the liver, such as itraconazole, ketoconazole, and HIV protease inhibitors, may be impaired by rifampicin. (59)

While there is a positive association between a higher dose of rifampicin and its bactericidal effect (60), in general practice, the dose has been restricted to 450–600 mg once daily, and somehow concerning body weight or liver function. This dosage provides the minimum inhibitory concentration against Mycobacterium tuberculosis. Another explanation is that the drug's adverse effect on liver function is positively correlated, which means that the adverse effect arises as the dosage is increased (61). To optimize drug absorption, it should be taken on an empty stomach (62). The red-colored urine is identified as a side effect of this medication that can surprise the patient. A further gastrointestinal impact is possible. Jaundice and disruption in blood cell development can occur in serious cases (63).

1.4.3 Isoniazid

Isoniazid exerts antibacterial activity by stimulating the peroxidative mechanism of the mycobacterial enzyme KatG, resulting in the development of NAD(+) and NADP(+), which inhibit lipid and nucleic acid biosynthetic enzymes. Mycobacterium requires the lipid layer to protect itself. The interference of this layer caused by isoniazid makes mycobacterium more susceptible to other drugs, especially those that operate intracellularly (64). Isoniazid is metabolized and excreted by the liver and kidney. Caution should be taken in those who have liver disease, as this may result in the prolonged metabolism of isoniazid, resulting in a detrimental impact. Isoniazid's well-known side effects include peripheral neuropathy, which is more prevalent when doses exceed 300 mg per day. This neuritis is reversible, and pyridoxine administration can relieve the symptoms. Moreover, some gastrointestinal upset has been recorded. Isoniazid should be taken on an empty stomach for optimum absorption. Isoniazid interacts with monoamine oxidase inhibitors (65), antacids, and any medication that needs cytochrome P450 (CYP450) system

metabolism, such as phenytoin and carbamazepine, diazepam, triazolam, theophylline, valproic acid, and disulfiram (66).

1.4.4 Ethambutol

Ethambutol sterilizes mycobacteria by interacting with the arabinogalactan found on their cell wall. This medication acts as an inhibitor of the arabinosyltransferase enzyme. Ethambutol, like any drug, is metabolized in the liver and excreted in the urine and feces. Unlike the other medication, Ethambutol does not require dose adjustment in patients with liver failure, while it is necessary to change the dose in patients with kidney disease. To minimize toxicity, antacids and ethionamide should be used cautiously when taking ethambutol (66).

1.4.5 Pyrazinamide

Pyrazinamide is a nicotinic acid derivative that acts as a bactericide by preserving the acidity level of the vacuole that comprises the lysosome, an enzyme involved in the degradation of mycobacterium in macrophage. This drug is passively delivered into bacteria, where it inhibits key enzymes such as fatty acid synthase I, which is crucial for the production of mycolic acid, a critical component of cell membrane structure. Pyrazinamide is excreted in the urine after being metabolized in the liver. Additionally, this drug can cross the blood-brain barrier. The most often seen adverse effects include hyperuricemia and hepatotoxicity. As a result, it should be tailored to the specific needs of the patient with liver dysfunction. Probenecid, rifampin, isoniazid, and ethionamide, or pyrazinamide all have the potential to interfere with this medication. Zidovudine can interfere with the action of pyrazinamide (66).

1.4.6 Fixed Drug Combination versus Separate Regiment

To improve compliance, Tuberculosis fixed drug combinations (FDCs) are also being prescribed in clinical settings as part of the national initiative, with some patients may receive a different regimen. Concerning effectiveness, a combined regimen may result in a higher rate of adverse effects, and a study demonstrates obvious visual side effects concerning patients receiving the fixed drug combination in both nondiabetic and diabetic patients, despite the need for further evidence (67). The disparity in smear conversion time between those who received the FDC and those who received the segregated tablet was evaluated in pulmonary tuberculosis (68). The meta-analysis, however, did not support the substantial difference results for some outcomes in pulmonary

tuberculosis, including failure, relapse, death, severe adverse effect, and sputum smear conversion (69). In summary, FDC and ST do not produce significantly different outcomes as long as the adherence is higher.

1.4.7 Adjuvant (Pyridoxine)

Neuropathy has been described as a normal, reversible, and avoidable adverse effect of tuberculosis treatment. Isoniazid functions as a competitive inhibitor of pyridoxine, thus disrupting physiological processes mediated by pyridoxine, including signal transmission in the neuron. As a result, mandatory pyridoxine supplementation has been incorporated into tuberculosis regimens (70).

1.5 Outcomes

The WHO has classified patients into two categories based on their infection status, each of which would receive separate treatment. These classes include the following (57):

- New patients who have never received tuberculosis care or who are now receiving tuberculosis treatment for less than a month.
- A previously treated patient is described as anyone who has been treated for tuberculosis and has been cured or completed treatment or has failed or been lost to follow-up (any patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more).

For tuberculosis in the lungs, which accounted for the majority of tuberculosis cases, The following outcomes are described by the World Health Organization (57):

- Cured tuberculosis is characterized as a patient with established pulmonary tuberculosis before treatment who has negative sputum smear or sputum culture results at the end of treatment and on at least one previous occasion.
- Treatment Completed refers to a patient who has completed medicine but has no proof of failure or an inaccessible record of sputum smear or sputum culture on the day of therapy completion. This is either due to a delayed examination or a failure to administer the exams. However, this patient should have at least one negative sputum test result.

- Uncomplicated case failure is characterized as a patient who develops a positive sputum smear or sputum culture results in the fifth or subsequent month of treatment. Any situation in which a positive result develops in the third month following a consecutive positive result in the preceding month is often considered a loss.
- A relapse is described as a patient who has been deemed cured or who has completed treatment but develops tuberculosis again, either as a re-infection or as a true relapse.
- Drug-Resistant
- Death

1.6 Drug-resistant Tuberculosis

1.6.1 Definition

Drug-Resistant Tuberculosis is an infection caused by a mycobacterium that can survive or remain viable if treated with a normal regimen. The WHO has described drug-resistant tuberculosis in specific terms, including (57) :

- Mono-resistance: a term that refers to the resistance of a single first-line anti-TB medication. If only ethambutol OR pyrazinamide is found to be resistant, this term is used.
- Isoniazid-Resistant is a term that refers to mycobacteria that exhibit resistance to isoniazid.
- Poly-resistance: resistance to more than one first-line antituberculosis drug, except isoniazid and rifampicin. This demonstrates that both ethambutol and pyrazinamide are resistant.
- Multidrug resistance (MDR) is characterized as the presence of resistance to at least two of the following drugs: isoniazid and rifampicin.
- Extensive drug resistance (XDR) is characterized as resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, or amikacin), as well as multidrug resistance.
- Rifampicin resistance (RR): phenotypic or genotypic resistance to rifampicin, with or without resistance to other anti-TB medications. It encompasses all forms of rifampicin resistance, including mono-resistance, poly-resistance, MDR, and XDR.

1.6.2 Epidemiology of Drug-resistant Tuberculosis

Since 2017, drug resistance screening has been promoted, and in 2018, approximately 51% of patients with bacteriologically confirmed tuberculosis were tested for rifampicin resistance, up from 41% the previous year. The WHO reported a total of 186,772 MDR/RR-TB cases identified and reported globally in 2018, an increase over previous years (71).

The disparity between detected cases and those who seek care continues to grow wider. Additionally, ten countries contributed approximately three-quarters of the global difference in MDR/RR-TB care enrollment in 2018, including China, India, Indonesia, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, and Vietnam. Due to their larger populations, China and India accounted for 43% of the global care enrollment gap (71).

The total number of drug-resistant tuberculosis cases is about 24000, with 9038 cases confirmed and only 4194 patients initiating care in 2018 (71). Indonesia's Ministry of Health registered 4413 drug-resistant cases without specifying the form of resistance. In 2018, the difference between observed and enrolled cases was 51%. This is compounded further by a dearth of diagnostic modalities for drug-resistant tuberculosis. To serve the 268 million population, there are currently 360 referral TB hospitals, 2304 primary care with radiology modality, 7326 microscopic laboratories, 936 rapid molecular diagnostic testing centers, 21 laboratories for culture, 11 DST laboratories, and 7 LPA laboratory. (19)

1.6.3 Treatment of Drug-resistant Tuberculosis

a. Isoniazid-resistant

For the isoniazid resistance, a 6-month course of rifampicin, ethambutol, pyrazinamide, and levofloxacin is recommended. Streptomycin and other injectable medications are not recommended if rifampicin is sensitive(72).

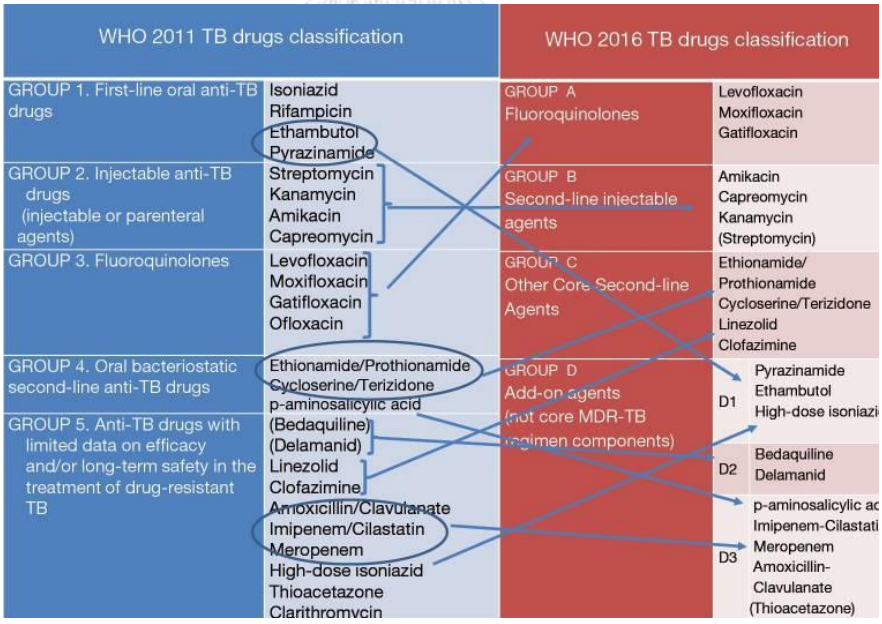
b. MDR/RR TB

Three drugs from group A and at least one from group B should be initiated, and the drugs from group A should be continued over the course of therapy until bedaquilline is discontinued. If no more than two drugs from

group A are available, two drugs from group B should be used. If four drugs from groups A and B are unavailable, a drug from group C can be used (72).

Some consideration was given to the fact that kanamycin and capreomycin are not approved for longer-term care of MDR/RR-TB patients, while levofloxacin, moxifloxacin, and linezolid are preferred. Bedaquiline is prescribed for patients over the age of 18 in longer MDR-TB regimens and is still permitted in children ages 6-17. On longer regimens, clofazimine, pyrazinamide, cycloserine, ethambutol, and terizidone can be used as a second-line preference. Delamanide is appropriate for patients aged 3 years and over. Pyrazinamide can be added to longer-term regimens for MDR/RR-TB patients. Amikacin is only given when a susceptible outcome supports its use; if Amikacin is not available, streptomycin can be substituted. If bedaquiline, linezolid, clofazimine, or delamanid are not available or a better regimen cannot be devised, ethionamide or prothionamide and para-aminosalicylic acid are preferred. Clavulanic acid should not be used in longer-term regimens (72)

Table 2.1 Tuberculosis Drug Classification showing the first line and other lines of the drug, some modifications of preference can be seen in 2016.



The length of treatment may vary between 18-20 weeks, and continuation for at least 15-17 months following culture conversion is recommended. 6-7 months of an intense period is recommended for amikacin regimens. The shorter

regimen is reserved for patients with MDR/RR-TB who have not been treated with second-line medication or who are resistant to fluoroquinolones. The period is between 9 and 12 months (72).

1.7 Associated Factors of Drug-resistant Tuberculosis

1.7.1 Sociodemography

Age can be a factor, as aging deteriorates the immune system. This is consistent with the theory that aging may result in a decrease in the production of B and T cells in the bone marrow. Adults and the elderly who have lost their thymus gland have also had problems with T cell maturation. This is often accompanied by a decrease in the maturity of these cells in lymphoid tissue. As previously mentioned, tuberculosis eradication requires B and T cells; therefore, aging may be a factor in tuberculosis remaining viable and developing drug-resistant genotypes (65).). Additionally, it is suggested that the decline in the turnover time of certain cells may affect the function of the tissue, such as an epithelial layer, resulting in a more vulnerable barrier, especially in the respiratory tract. Although some research established older age as a risk factor for drug-resistant tuberculosis, others found contradictory findings. A study in Botswana (73) and Oman (74) found that people under the age of 20 have an Odd Ratio of developing drug resistance as high as 6.80 (95 percent confidence interval 1.6128.75, p 0.009), although other studies emphasize that people over the age of 40 are more likely to develop drug resistance (75) (76) There is an implication that younger age is more vulnerable, most likely due to treatment adherence, unhealthy activity, or increased interaction with other people.

Males, in particular, are predisposed to drug resistance. There is a hypothesis that accounts for this disadvantage. Males are more likely to indulge in unhealthy behaviors such as smoking, working, and socializing. Males are more likely to develop drug-resistant tuberculosis than females, although the risk is negligible (OR 1.07 (0.85–1.36)(11).

Education level is important because it influences the health belief model. The perceived risk of tuberculosis and the benefit of cough prevention and medication use could influence their decision about tuberculosis treatment. According to a report, patients without a formal education have an increased risk of developing drug resistance by up to 1.63 times [Adjusted Odd Ratio 95 percent CI = 1.03-3.11] (77)

When the world's attention has shifted to how health care should be made available and affordable to all people, the availability of health insurance has become pivotal, as those with health insurance coverage can receive adequate treatment at the appropriate time, delaying the complication that is almost certain to occur. Indonesia has implemented a health care scheme based on the Bismarck model, in which all citizens would be covered for the entire direct cost of a particular program, such as tuberculosis by paying a premium. According to a study conducted in China, individuals who lack insurance are up to 1.99 times (1.12-3.54) more likely to develop drug-resistant tuberculosis (78). Income has a direct correlation with people's ability to afford diagnostic testing and medication. Individuals with lower incomes may face financial hardship and have a lower rate of commitment to therapy due to the cost of prescription medication. Although the national initiative has covered the direct cost of care. Indirect costs, such as transportation to the health clinic, continue to add to the patient's burden.

Marital status may play a role, but not because of the government-recognized status, but because of the status that enables them to live with their spouse or alone. There are two ways in which marital status can influence drug-resistant tuberculosis. An individual who lives alone may experience worse outcomes because they lack a caregiver to care for them or to remind them to take their medication; this is especially true for people who are elderly or have a very busy schedule. However, individuals who live with a partner can contract drug-resistant tuberculosis if they have close contact with a positive drug-resistant partner. Research conducted in Malaysia found that unmarried patients are up to 2.58 times more likely to develop multidrug-resistant tuberculosis (79), Combining evidence from studies conducted in Houston, Pakistan, and Malaysia, the study emphasized the fact that married people are protected from drug-resistant tuberculosis, but the protection is not statistically significant (OR 0.64 95 percent CI 0.13-3.11). (11).

Employment status has a variety of implications for drug-resistant tuberculosis. It may affect disease transmission, and people with jobs may avoid financial distress if they become ill. Individuals may contract the disease at their place of employment, especially from sick coworkers, and may be worsened by unsafe work conditions such as inadequate ventilation, exposure to an inhalant chemical, and so forth. However, individuals with secure employment, especially those with a steady income, will cover their health costs either by personal spending

or as a benefit from their employer, and can ultimately receive adequate care when they become ill. According to some reports, unemployment contributes to drug resistance, as seen in Burkina Faso (80) and Brazil (81)

1.7.2. Factors Related to Immunity of the patient

The presence of diseases can impair patients' immunity, thus jeopardizing tuberculosis eradication. Several diseases are associated with impaired immunity and drug-resistant tuberculosis, including the following:

a. Diabetes

Individuals with diabetes may have a distinct immune system and inflammatory response profile. This group exhibits a steady increase in the number of leukocytes, including granulocytes and monocytes, as well as increased expression of IL-1RA, IL-18, and fibrinogen. This may result in an imbalance of pro- and anti-inflammatory cytokines. Increased pro-inflammatory cytokine production as a result of a greater number of leukocytes expressing these cytokines will result in remarkable tissue damage (82).

Unsurprisingly, the proliferation of leukocytes is not proportional to their efficacy. In patients with diabetes, macrophage phagocytic activity is usually lower than in patients with normal glycemic regulation. This could result in mycobacteria surviving, allowing them to adapt to immune systems and evolve a drug-resistant gene. This was shown in an in-vitro study using bone marrow cells, where a decreased phagocytic activity was observed. The length of exposure to high blood glucose also affects cytokine expression, with short-term exposure increasing IL-1 expression and long-term exposure increasing both IL-1 and TNF expression. Additionally, this could result in a decrease in the production of IL-12p40 and nitric oxide by M1 macrophages, both of which are needed for mycobacterium eradication. TNF elevation is associated with an increase in Matrix Metalloproteinase (MMP) expression, which is responsible for tissue remodeling and structural changes in the respiratory tract. (83) In short, diabetes will prolong the mycobacterium's intracellular viability.

The deficiency of phagocytic activity is reversible, as shown in a case-control study of 42 participants, where the inverse association between fasting blood glucose, HbA1c, and mononuclear cell phagocytic activity was observed. This is based on the assumption that people with diabetes who have their blood glucose under control have a fully functioning immune system (84).

Another factor that correlates with drug-resistant tuberculosis is pharmacokinetic. An analysis shows a 53 percent reduction in rifampicin concentration in a patient with diabetes mellitus. Additionally, there is no dose change in a clinical setting for tuberculosis patients with diabetes. Exposure to concentrations less than the minimum inhibitory concentration will result in the development of drug-resistant tuberculosis, most notably rifampicin-resistant tuberculosis (85). There may be some interaction between oral anti-diabetics and tuberculosis regimens, but no conclusive proof exists. Insulin is the preferred diabetes treatment for tuberculosis patients since it does not interfere with the tuberculosis regimen.

According to the explanation above, it appears that, despite having diabetes, these individuals can maintain an optimal immune system as long as their blood glucose is under control. The glycated hemoglobin A1c has been commonly used as a method for determining the glycemic profile, as it can represent the average blood glucose over the previous three months. Additionally, the HbA1c level can be used to predict some complications of diabetes. (86) This test has been standardized, for example, by the NGSP, and is considered suitable for diabetes diagnosis and follow-up therapy (87). In Indonesia, those with national health insurance are eligible for free HbA1c screening. Diabetes screening is also performed on tuberculosis patients, referred to as bi-directional screening. Diabetes, according to some reports, can increase the risk of developing drug-resistant tuberculosis by up to 3.4 times [CI = 1.96-5.16]). (77) Following several meta-analyses, the risk of diabetes patients developing MDR-TB is as high as 1.83 (95% confidence interval [CI]: 1.45–2.31) (88) and even higher when many confounding variables are taken into account (OR = 2.43, 95% CI 1.90 to 3.12). (89).

When it comes to the ethnic composition of this diabetes population, Caucasians are the most susceptible, followed by Asians. This may mean that factors such as geography and ethnic origin could play a role in drug-resistant tuberculosis. Subsequently, diabetes is a risk factor for developing primary MDR-Tuberculosis but not for secondary MDR-Tuberculosis (88). To summarise, diabetes can affect drug-resistant tuberculosis, but it is not the only factor. Drug-resistant tuberculosis can be predicted by evaluating both disease treatment and glycemic profile.

b. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease that causes shortness of breath and chronic coughing as a result of respiratory tract obstruction. In spirometry, this is referred to as a decreased forced expiration volume. These anatomical changes can impair the respiratory tract's barrier to foreign bodies and bacteria, making it susceptible to respiratory disease. Additionally, people with COPD exhibit a loss of CD4 T cells. According to a study conducted in China, approximately 14.2% of people with COPD develop MDR tuberculosis. Drug susceptibility testing demonstrates that individuals with COPD developed monoresistance, INH resistance, Rifampicin resistance, and Fluoroquinolone resistance, and this population is prone to re-infection (90). According to a meta-analysis, people with COPD are at an increased risk of developing multi-drug resistance by up to 2.53 times (CI 1.05-6.14) (11).

c. People with Human Immunodeficiency Virus (36)

HIV-infected individuals have a weakening CD4 lymphocyte activity, which is critical for the immune system. A meta-analysis of 24 observational studies found that HIV is associated with MDR TB (Pooled OR 1.24; 95% CI: 1.04–1.43) and a higher risk of developing primary MDR-TB (Pooled OR 2.28; 95% CI: 1.52–3.04)(91). Moreover, people living with HIV have a lower cure rate for MDR-TB Which may increase secondary drug-resistant tuberculosis transmission and mortality (92).

In terms of antiretroviral and antituberculosis medication interactions, rifampicin's hepatic elimination can interact with antiretroviral drugs such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (93) because these drugs inhibit and induce the CYP 450 enzyme, respectively, whereas other drugs such as isoniazid, ethambutol are not. This may imply that the rifampicin and antiretroviral therapy dosages should be adjusted accordingly; otherwise, the minimum inhibitory concentration may not be reached (94).

d. Body Mass Index

The body mass index can have a variety of associations with drug resistance. In comparison to BMIs less than 21 kg/m2, a higher body mass index is associated with increased expression of pro-inflammatory cytokines such as TNF alpha, which can cause tissue alteration (95). Interestingly, while there is a significant increase in leukocytes,

especially lymphocytes, as BMI increases, this increase is not accompanied by the activation of these cells (96). With regards to the lower BMI, it is assumed that the lower BMI is a result of tuberculosis infection and can have an effect on the outcome, such as delayed sputum conversion.

The body mass index can affect the drug's pharmacokinetics. In Turkey, a study found an inverse relationship between isoniazid serum concentration and body mass index(97). Another research discovered that patients with a high body mass index had a lower rifampicin concentration (98). As shown in an Ethiopian study (99), body mass index is not correlated with MDR-TB, and a meta-analysis confirms these negligible results (OR 0.86 (0.17–4.27)(11).

e. Smoking

Smoking has several detrimental effects on the respiratory tract, including enlarging mucous glands, obstructing narrow airways, and resulting in emphysema. This is because of the oxidative stress caused by smoking's gas process, which can result in epithelial injury and the release of proinflammatory cytokines. Smoking repeatedly results in impaired tissue remodeling as a result of a functional proteolytic imbalance within the inflammatory response elicited by tobacco smoke. This deficiency results in altered respiratory tract function and distal structure enlargement, resulting in a less strong barrier and mucous accumulation, which provides an ideal habitat for a microorganism to replicate (2). Smoking is associated with multi-drug resistant tuberculosis (AOR = 2.56 [CI = 1.19-3.26])(77), but the association varies, depending on the length and quantity of cigarettes smoked.

f. Alcohol consumption

Alcohol consumption can result in abnormal liver function, which is referred to as Alcoholic Liver Disease. The liver metabolizes alcohol through the enzyme CYP2E1, which catalyzes the oxidation of ethanol to acetaldehyde. This enzyme is involved in isoniazid metabolism. This can cause isoniazid hepatotoxicity when combined with rifampicin (100). Consequently, changes in liver tissue arise as a result of alcohol intake. Steatosis is the initial stage of heavy drinking in which fat is accumulated in hepatocytes; it progresses to steatohepatitis, fibrosis, and finally cirrhosis, which affects not only liver cells but also adjacent structures such as blood vessels (101).

Alcohol is a risk factor for Multi-Drug Resistant Tuberculosis, according to a report conducted in Botswana (102). On the other side, a meta-analysis reveals that the results are insignificant. (OR 0.80, 95% confidence interval 0.49-1.30). It seems as if the occurrence of binge drinking episodes is more significant than determining the average amount of standard drinking. Alcohol consumption is prohibited in Indonesia and is not accessible in public establishments, as alcohol consumption is prohibited by religion.

g. Immunosuppressant use

The glucocorticoid is commonly used in medicine and for off-label applications such as doping. Glucocorticoids function through their receptor (glucocorticoid receptor/GR) to induce a variety of immunosuppressive responses. In a mouse model with a higher GR level, decreased thymic cellularity is accompanied by increased glucocorticoid sensitivity of thymocytes. This can induce T cell apoptosis, particularly in the peripheral system, while also inhibiting T cell migration. Additionally, glucocorticoids impair macrophage differentiation and dendritic cell maturation, both of which are required for innate immunity (103). There are some disagreements about how long glucocorticoids can affect the immune system, but a higher dose administered for more than three weeks can impair the immune system (104), and some particularly susceptible groups include those who take long-term steroids, such as those with asthma, COPD, or who undergo organ transplants.

Another strong immunosuppressive agent, such as anticancer medication, can immediately impair the immune system. Chemotherapy inhibits the development of blood cells, including leukocytes, in the bone marrow. The primary goal of chemotherapy in cancer is to boost cytotoxic immunity while decreasing tumor vascularization through interaction with Vascular Endothelial Growth Factor (VEGF). However, this effect is not specific and can affect healthy tissue, resulting in decreased tissue function and creating an infection-prone environment (105).

h. Presence and adherence to previous treatment.

Patients with a prior history of tuberculosis care may have a lower rate of adherence due to the regimen's complexity and length. Occasionally, a patient will discontinue their medication as their condition improves; this is referred to as drop out. According to a report, treatment drop-out will result in multidrug-resistant tuberculosis (AOR = 8.86 [CI = 5.45-11.2]) (77). This is most likely due to a decrease in the inhibitory concentration of the drugs in the

blood, which forces the pathogen to adapt and evolve the resistant gene. As shown in Botswana, the existence of prior TB treatment increases the risk of developing multidrug-resistant tuberculosis by 7.24 times (73) If the final result is withdrawal or failure, this equates to a 5.6-fold risk of contracting MDR-TB (11).

i. History of Adverse Tuberculosis Drug Reaction

Due to the possibility that tuberculosis drugs can cause gastrointestinal upset, skin reaction, red-colored urine, neuritis, joint pain, or jaundice, a physician can adjust the prescription to address this condition. The experience of developing adverse reactions can also increase the patient's hesitancy and reluctance to continue medication. Likewise, medication modification can affect the minimum inhibitory concentration in comparison to the regular regiment. According to a report, any history of adverse effects increases the risk of developing multidrug resistance, as seen in China (76).

j. History of drug/substance abuse

Individuals who abuse drugs or alcohol can engage in risky behavior, including the use of injectable drugs together with other people. This may result in HIV transmission, thus impairing the immune system. Individuals that misuse drugs and alcohol are at risk of malnutrition, making them susceptible to infection. An analysis discusses the impact of opiates on immune function, since this drug directly activates opioid receptors on immune cells, including μ-, κ-, and δ-opioid receptors as well as nonclassical opioid-like receptors. This interaction can result in a decrease in phagocytic and natural killer cell activity. Another mechanism is that this drug can modulate glucocorticoid release, which affects both the cellular immune response and the release of transforming growth factor beta induced by the central opioid pathway. Cannabis also affects NK cell growth, while cocaine inhibits lymphocyte proliferation (106). According to a review, this group is more likely to have latent tuberculosis infection, which may reactivate at a later date. If they become infected with drug-resistant tuberculosis and develop latent tuberculosis, this primary drug-resistant tuberculosis will reappear at a later stage (107). Individuals who misuse drugs may gain their first exposure to narcotics while in imprisonment; therefore, there is an assumption that the substantial association between incarceration history and multidrug resistance may be explained by this assumption (11, 79).

k. Presence of other Chronic Disease

Chronic diseases such as hypertension, stroke, and heart disease may all have an impact on tuberculosis treatment and outcome. Individuals with chronic conditions may have decreased activity levels, making them more reliant on others to perform everyday tasks. Individuals who have suffered a stroke can be unable to walk or even eat normally. This could make the prescription process more difficult. Thusly, drug interactions between medications for various diseases are unavoidable. No research specifically addresses this assumption with drug-resistant tuberculosis.

1.7.3 Disease Severity

Several studies have successfully determined which tuberculosis strain is the strongest and causes the most extreme manifestations; one of these strains is the Beijing strain, which is associated with drug-resistant tuberculosis (11). However, in practice, strain identification is rare, and the seriousness of the disease is a product of a combination of factors. Thus, defining the clinical manifestations will provide a rough estimate of the mycobacterium's strength as an agent and its resistance propensity.

a. Level of Sputum Smear

The degree of smear suggests that mycobacterium has a greater capacity for replication. The bacillary index has been used to grade the seriousness of the disease, most notably in pulmonary tuberculosis sputum smears. Numerous studies have been conducted to determine the association between delayed sputum conversion and drug resistance. Research conducted in Ethiopia demonstrates that a higher smear level is correlated with MDR-TB (108) and this association is supported by a meta-analysis (11).

b. Radiology Features

A characteristic of radiology, especially chest radiology, is the manifestation of anatomical changes caused by an immune response to mycobacterium. An extensive lesion means that the pathogen has spread widely, as shown in a study demonstrating that MDR-TB has an extensive lesion(109). Certain characteristics, such as cavities, require an advanced immune response. A cavity forms as a result of the granuloma encasing the mycobacterium. This entrapment results in a low oxygen environment, which results in liquefaction necrosis that appears as a cavity on

radiography. A resected cavity reveals the presence of several drug-resistant mycobacteria, as shown in Georgia (110) This demonstrates that patients with cavities are often drug-resistant.

1.7.4 Environment factor

The environment is divided into two components: the optimal environment for replication and the ease of transmission. Interaction with a positive case is a risk factor for tuberculosis and drug-resistant tuberculosis. This could be exacerbated if a greater number of people are crammed into a smaller room. According to a study on Rebreathed Air Volume (RAV) (111), higher RAV (300–1000 liters/day) may contribute to tuberculosis transmission through super-spreaders or people with tuberculosis disease (exhaling more than 10 infectious doses/day) and people with low infectivity (exhaling less than 10 infectious doses/day), whereas lower RAV contributes This can also explain why individuals in prison are vulnerable to tuberculosis. Ventilation may be involved in this scenario due to its impact on the RAV. Meteorological factors have been implicated in tuberculosis transmission. A study conducted in China indicates that TB transmission can be predicted with a two-month lag in temperature data and a three-month lag in humidity, total precipitation, and sunshine. Both variables are inversely related to tuberculosis incidence (112). However, since it is located in a tropical region, these factors fluctuate less than they do in China, indicating that this factor is less likely to have led to tuberculosis.

1.8 Economic Burden of Drug-Resistant Tuberculosis

The burden of Drug-Resistant tuberculosis varies according to treatment period and the form of drug-resistant tuberculosis. A 2017 multicenter study in Vietnam found that the direct cost of Multidrug-Resistant Tuberculosis was linked to pharmaceutical and material components. A nine-month treatment plan costs US$1480.34 211.61 and a twenty-month regimen costs US$2695.58 294.98 (113). Subsequently, an analysis in China demonstrated a loss of efficiency of approximately 2615 Chinese Yuan or 373.9 US dollars in currency exchange. (114)

The cost of diagnosis was also included in the direct cost calculation. The cost of diagnosis was estimated in three countries, Indonesia, Kazakhstan, and Ethiopia, as the cost per diagnostic visit, which included registration fees, laboratory testing, medications, food, lodging, and transportation. Patients in Indonesia were seen 2-4 times for

diagnosis, with the majority of the cost going toward travel, food, and laboratory testing, which can cost up to 46 USD to diagnose MDR tuberculosis (15).

Laboratory diagnosis consists of many components that vary according to the method of testing, including a rapid test (gene Xpert), a drug sensitivity test, and a sputum smear. Additional testing may be necessary, such as screening for other diseases, such as diabetes, and mandatory HIV testing. The drug susceptibility test costs ranging between 23 and 41 USD, depending on the country of origin (Moldova, South Africa, or India), but the price varies according to the pay of the laboratory technician, the price of the diagnostic kit (which heavily influenced by import prices), and the type of culture medium used (MODS or MGIT) (115). According to a study conducted in China, the cost of Gene Xpert is very high. A single assay, which costs 22.82 USD, is adequate to detect rifampicin resistance. The incremental cost was found to be higher when the second time assay was used to detect drug resistance in a patient with pulmonary tuberculosis and even higher in extrapulmonary tuberculosis, reaching up to US$291.87. It is important to reduce the diagnostic burden in drug-resistant patients (116)

2. The Artificial Intelligence in Medicine

Although there is no precise definition of Artificial Intelligence (AI), it is a widely held belief that artificial intelligence is a class of modalities that function by simulating human thought and behavior in response to a challenge. In a nutshell, artificial intelligence aims to relieve humans of the responsibility of solving everyday problems such as decision-making or other practical issues. Medical practice is now integrating a bigger portion of Artificial Intelligence (117).

In medicine, artificial intelligence is classified into two subfields: physical and virtual aspects. The physical component of AI includes applications such as nanosurgery, robotics, distance surgery (in which the surgeon performs surgery in a remote location and the order is fulfilled by a robot), and AI to assist with medicine and caregiving services. Another term for this is virtual AI, which refers to the precision with which decisions and algorithms are made. One of the patient safety targets is punctuality in diagnosis and care. Historically, physicians could rely on their judgment after many years of training. This is possible because diseases can exhibit a pathognomonic pattern of signs and symptoms. The simple algorithm then develops into what is known as a scoring

method, which becomes an early form of artificial intelligence. This straightforward algorithm generates basic inferential statistics. Since the health service already uses an electronic records system, an easily accessible and accurate source of data can be used to establish a general pattern of illness, and the presence of a computer facilitates pattern recognition. (118) It is believed that this artificial intelligence would ultimately outperform advanced modalities and even physicians, thus reducing bias and mistreatment.

2.1 Decision Making in Medicine

In certain ways, the foundation of medical decision-making is based on the theory of the conventional method. This theory is axiomatic in nature, in that it considers the likelihood and uncertainty of optimal expected outcomes (for example, by the use of Bayesian inference) following the theory or the normative. This results in predetermined rules and outcomes.

The following are some examples of factors that influence decision-making. Due to the appendix's predominant location in the lower right quadrant of the abdomen, pain emanating from this region is suggestive of appendicitis. At this point, certain judgments about particular variables have shifted away from the normative or the theory learned by a practitioner. This may add prejudice and lead to mistaken judgment if it is solely based on this previously acquired experience. Additionally, in women, the probability of right lower quadrant (RLQ) pain may not be solely due to appendicitis; another adjacent organ, such as the ovarium, may have an abnormality, resulting in RLQ pain. This is referred to as conceptual knowledge, and it is the process by which a physician acquires all relevant information, incorporating the new idea into their established knowledge. By doing so, the practitioner will aware that not all signs and symptoms can manifest in any patient, resulting in what is known as the probability theorem. If only one symptom is present, a physician will consider the likelihood of the outcome. Additionally, the practitioner gains knowledge from each case they treat. A physician who has been exposed to the correct diagnosis has an increased possibility of making the correct diagnosis. Interestingly, there is a concept called natural decision making, which refers to decision-making that is influenced by the environment in which the decision is made. Medicine is an area where stress occurs as a result of the expectation of rapid decision-making; this, by far, will motivate the practitioner to narrow down the possible tests that will provide a clearer response (119).

By preventing the bias from this subjective decision-making, decision-making has been directed to technology-mediated decision-making. This is the field in which modern technology is supposed to solve problems. The machine will benefit from both the flowchart and the database that are now accessible electronically. The flowchart indicates that the machine will process the information collected during the history-taking process and the findings of the medical test, presenting the desired definite outcome. The flowchart method can make use of a large amount of data to discover and recognize a pattern. This is the underlying principle of technology-mediated decision-making. Additionally, the database approach is frequently used to translate certain types of multidimensional data through deep learning and pattern recognition. For instance, detecting tuberculosis accurately in a series of tuberculosis chest X-ray images (120).

The Alvarado Score for appendicitis is a basic pattern recognition in decision-making using the flowchart approach. A systematic review demonstrates that by retrieving only information on signs, symptoms, and laboratory values (migrating pain, anorexia, nausea, tenderness in RLQ, rebound pain, elevated temperature, leucocytosis, and change to the left of white blood cell blood count), this score can rule out appendicitis at the cut-off point of 5 in all patient groups, despite some variation and overfitting in a woman. The LOESS feature is often used to establish this form of clinical scoring. (121).

2.2 Artificial Neural Network in Medicine

Artificial Neural Networks, or ANNs, are a subset of artificial intelligence that perform functions similar to those that regression can perform. ANNs are capable of dealing with data complexities and problem-solving, generalizing the pattern of the data to produce robust and rational estimation. Unlike other statistical methods that require assumptions, ANN can deal with complex interaction in some sample data, deal with nonparametric assumptions, and explain the subtle relationship between some parameters, especially when some theory is insufficient to explain the plausibility of a case (122).

The structure of the ANN is similar to that of the neuron in the human brain, with nodes (representing the neuron) connected to other nodes through iterative measurement. The feed-forward neural network (FFNN) and the recurrent neural network are two types of ANN. The distinction is in the direction of knowledge flow. The FFNN

transmits information in a single direction from input to hidden layer to output, while the recurrent neural network (RNN) incorporates feedback loops. The FFNN model will produce a single output, while the recurrent neural network will produce multiple outputs as the feedback mechanism affects the adjustment of "weight." The FFNN model is often used in medicine, especially for diagnosis, as it provides straightforward answers such as yes or no disease, although the RNN model can also be used for classifiers, as shown in a study to predict 30-day readmission for heart failure, where it outperformed the FFNN and logistic models (123).

2.2.1 Elements of Neural Network

There are many words used to describe the learning process in ANNs. Supervised, unsupervised, and reinforcement learning are all forms of learning. When all parameters are correlated with a specific output, this is referred to as supervised learning. For example, by providing an input source such as egg, milk, and flour, we can determine if this input can be used to make pancakes or not. Thus, the response is either yes, it will be a pancake, or no, it will not be. The predicted output of unsupervised learning, the ANN, is not always the desired output, for example, by providing the same milk, egg, and flour, the model will produce cupcakes, omelets, and so on. No output is expected for reinforcement learning (124).

Although the ANN may have a single or multiple layers, it is typically divided into three layers: input, hidden layer, and output. The information contained in the input is multiplied by the weight of the neuron and bias is applied. The summation of bias and modified feedback will be triggered and transferred to the next layer of neurons via an activation mechanism (122).

The definition of the activation mechanism is now adopted. The activation function, also known as the transfer function, is a mathematical equation that specifies the output of the nodes specified in the input. This is critical in determining the type of output that will be transmitted. Additionally, depending on the application, the activation function assists in normalizing the performance of the nodes to a defined range. The binary phase function is an example of an activation function. This binary function returns a value between 0 and 1. Any bias and modified input summation that is closer to zero is graded as zero, and vice versa.

There are three types of activation functions that are often used: binary, linear, and nonlinear. The binary is often used when the desired response is binary (yes or no, good or bad) and cannot accommodate multiple outcome categories. The linear activation function is analogous to linear regression with a continuous output. The nonlinear one is more suited to dealing with data complexity, especially multidimensional data.

The sigmoid, hyperbolic tangent, softmax, and rectified linear unit are just a few of the activation models included in this group. Which activation function should be chosen is determined by how the data is likely to behave. The nonlinear model is preferred because it more closely approximates the predicted outcome in a real-world environment. The sigmoid and hyperbolic tangents are often used when dealing with classification, but they introduce certain advantages and disadvantages (125). The sigmoid activation function generates a continuous gradient rather than a binary phase, which may simplify the prediction. Extreme values, such as those greater than or less than 2, will add the final output value to the curve's edge, either 1 or 0. The fact that the sigmoid function has a minimum value of 0 and a maximum value of 1 indicates that this activation function is not zero-centered, and thus all values in nodes less than zero are considered zero. Additionally, a very high or very low value of X results in a vanishing gradient problem, indicating that the prediction remains unchanged. While the hyperbolic tangent can facilitate inputs or values with extreme values less than zero due to its range of -1 to 1, it also introduces the vanishing gradient, just as the sigmoid activation function does (125).

While the rectified linear unit is similar to the linear, it has a derivative activation function and supports backpropagation. This activation function converts the value to a linear unit, thus preventing the gradient from disappearing. However, as previously said, a negative input value will always be treated as 0. To address this, a modification called the leaky Rectified Linear Unit was developed. Softmax as the activation function produces a broader output than the sigmoid function and is thus suitable for classifying more than binary classes (125).

Normalization is a concept used in neural networks that is distinct from the normalization of data distribution. Normalization in a neural network is known as the process of transforming some input variables into a nearly identical range of intervals. This implies that input with a broad range of intervals, such as continuous data, is supposed to contain at least one narrow interval. The term discretization refers to the process by which various types

of data are regrouped into a single group. However, normalization should occur if discretization of data is not possible. This process can result in improved prediction, although it is not always the case. The three most frequently used techniques are the Z-Score method, the Min-Max method, and the median method. By measuring the arithmetic mean and standard deviation of the input variable, the Z score method "translates" the input value into normalized results. This could result in the mean value being set to zero. The Min-Max approach makes use of the input variable's minimum and maximum values. The median approach normalizes data using the median of each input. Several studies have compared the effectiveness of normalization and concluded that Min-Max can outperform normalization. If the raw data are normally distributed across the interval range, normalization may be unnecessary. Normalization is also determined by the quality of the data (126).

Imbalanced data class is another term that can affect the prediction outcome in a neural network. When the amount of data in a particular class is insufficient, it is referred to as an imbalanced data class. For instance, the number of positive cases is insufficient in comparison to the number of negative cases. This may result in a model prediction that is biassed against the majority class. Additionally, in medicine, such unusual cases can be classified as an imbalanced data class. There is a method for dealing with the data class that is out of control. The first approach is at the data stage, which eliminates the oversample majority class or adds any undersample minority class. Reduced sample size can affect the learning process with previous data while adding undersample data can cause the model to overfit. There is a mathematical technique that can be used to account for the probability of overfitting. The majority class can be eliminated using the K-Nearest Neighbour method, which allows for the omission of data far from the minority. For the undersample or minority class, the Synthetic Over Minority Sampling Technique (SMOTE) is used to generate some synthetic instances. The second approach is the algorithm method, which is based on increasing the cost matrix by setting a classification threshold for the sample or on a combination of the two (127).

Backpropagation is the process by which a neural network determines the optimal weight for each neuron to obtain the most accurate prediction; it can be based on how the activation function's derivates perform. The first step is to adjust the weights of the input pattern and send it to the hidden neurons, followed by activation computation and transfer to the output neuron, where the weights are adjusted to represent the output responses. The second step

involves comparing the output response to the desired output, which results in the creation of an error term. Following that, the error term is used to adjust the weights and biases of the network. The learning rate, the derivative of the activation function, the error term, and the current activity at the input layer all influence this modification. The following step is to compute the error for each hidden unit that sends data backward from the output unit. Finally, using a similar equation from the output layer, the weight of the input to the hidden unit is set (128).

2.2.2 General structure and layer

There is no universally accepted criterion for the layout of ANN, as long as it accurately predicts the result. A feed-forward neural network (FFNN) may be appropriate for basic decision-making (such as binary response), while another study needed a more sophisticated structure. The radial basis function (RBF) and multi-layer perceptron are the two most frequently used FFNN structures (MLP). The RBF is sometimes referred to as a shallow MLP because it contains only one hidden layer, while the MLP is referred to as a deep-learning network.

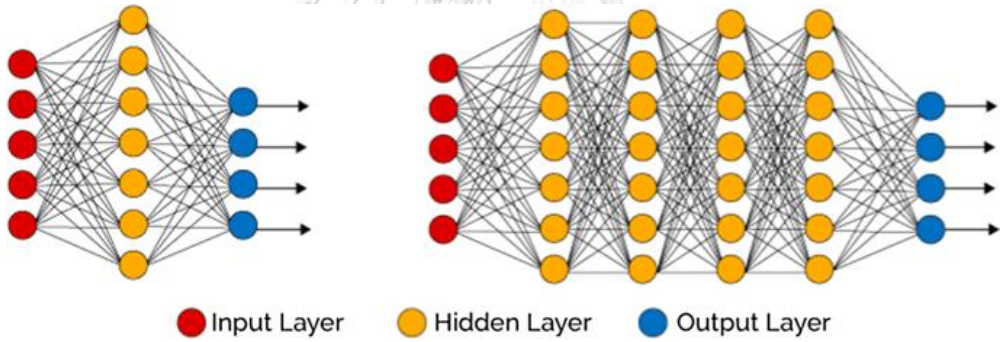


Figure 2.3 the RBF and MLP structure

It is important to understand the structure to make more accurate predictions. The hyperparameter specifies the type of external parameter that the operator intends to use. Several aspects of hyperparameters include the following:

- Number of Hidden Layers

  Numerous hidden layers can be modified using a forward method that begins with a small number of hidden neurons, while a backward method begins with a large number of hidden neurons. Certain guidelines exist, such as the range between the size of the input layer and the size of the output layer, or

approximately 2/3 of the size of the input layer plus the size of the output layer, or no more than twice the size of the input layer. Additionally, the number of hidden neurons should be equal to the number of inputs and outputs. The two-phase approach employs a group of data sets, with the first group being used to train the neural network, the second group being used to evaluate the network, and the final group being used to predict the performance. The smallest possible error is taken into account when determining the optimal number for the hidden layer. The final method is a sequential one in which hidden neurons are added one by one until the least error network is created (129).

- Dropout of neurons

  The term "neuron dropout" refers to the process of reducing or omitting some nonfunctional neurons to minimize the overfitting model. The way to determine which neurons should be dropped is to weigh their probability of independent entities. A probability of 0.5 is sufficient for the output node to be retained, while a probability of 0.8 or greater is needed for the input node to be retained. This technique is advantageous, especially for smaller datasets (130)

- Activation function (already explained)

- Weight Initialization

  Weight is the unit of adjustment for each input in a node. There are several weight initialization techniques, one of which is zero initialization, in which the weights of all neurons are set to zero. Random initialization is a technique in which all neurons are assigned random weights with a mean of zero and a standard deviation of one, implying that the value of the hidden node would be greater or less than one, requiring the activation function to exert very little effort to alter. Another technique is the Xavier Method, which is based on a node's variance (in terms of 1 per number of nodes), The He-et-al method differs slightly from the Xavier method, which initializes the weight by multiplying it by two. An analysis establishes that the he-et-al approach is more accurate (131).

- Learning rate

  The learning rate indicates the rate at which weight is updated during training. Simply put, this is the degree to which the neural network adapts its structure. The issue with the learning rate is that there are too many

training samples, too many neurons, and an unnecessary amount of computation. The learning rate is often set to be between 0 and 1 milliseconds (132).

- Epoch, iterations, and batch size

  A single epoch is known as the transmission of all data to and from the neural network. A complete data set should be passed through several times to allow the neural network to learn and produce the best prediction, but this is difficult when the data is large. A batch is a division of a dataset that allows it to move through a neural network on a smaller scale. The batch size parameter specifies the total number of training examples included in a single batch. Iteration refers to the number of batches needed to complete a single epoch. If the data set contains 5000 examples and the batch size is set to 500, the number of iterations needed to complete one epoch is 10. When data is too big to process in one go, this Epoch, iterations, and batch size should be considered (133).

Manually changing the factors above can be accomplished by trial and error, grid or random search, or Bayesian optimization. These functions are available in the current deep learning program in the form of a library. In medicine, both the Recurrent Neural Network (RNN) and the Convolutional Neural Network (CNN) are commonly used to achieve more complex outcomes. RNNs are typically used to classify more complex results, such as text and audio recognition, while CNN's are typically used for image classification, most notably when dealing with radiology features (122).

c. Model Selection and Validation

Following the model development, the best model is chosen based on its predictive performance. Several approaches for evaluating classification estimation include regression metrics or performance on real data. Given that neural networks are a subset of regression models, regression metrics such as the following can be used to determine the best model :

- Mean absolute error is defined as the average of the difference between the predicted and observed values.
- The root means squared error (RMSE) is the square root of the average of the squared differences between prediction and observation.

- The R2 is a statistic that indicates the percentage of variance explained by an independent variable or variables in a regression model. (134)

The model's performance on real data is measured by how well it predicts the given dataset, especially when used for classification purposes. Several straightforward techniques include the following:

• Classification Accuracy. This is the method for determining the model's accuracy by dividing the percentage of all accurate predictions by the total number of data points evaluated for prediction.

Table 2.2 Example of The Confusion Matrix

Variable	Disease	Absent of Disease
Predicted (+)	A	B
Predicted (-)	C	D

• The uncertainty matrix is a technique for determining true positive, true negative, false positive, and false negative

Some terms can be derived from this matrix :

Sensitivity : True Positive/ (True Positive + False Negative) or from the box = A / (A+C).

Specificity : True Negative / (True Negative + False Positive) or from the box = D / (D+B)

Positive Predictive Value : True Positive/ (True Positive + False Positive) or = A / (A+B)

Negative Predictive Value : True Negative/ (True Negative + False Negative) or = D / (D+C)

One thing that can be found in this confusion matrix is that the PPV and NPV values are influenced by disease prevalence. Thus, it is important in data testing to maintain a balance between the number of diseases and the number of no-disease cases, which is difficult to achieve. This is demonstrated by simulation using this table.

Table 2.3 Confusion matrix of disease with a prevalence of 25%

Variable	Disease	Absent of Disease
Predicted (+)	20	5
Predicted (-)	5	70

The PPV from this is : 20 / (20+5) = 80%

The NPV from this is : 70 / (70+75) = 93%

Table 2.4 Confusion matrix of disease with a prevalence of 50%

Variable	Disease	Absent of Disease
Predicted (+)	40	5
Predicted (-)	10	45

The PPV from this is : 40 / (40+5) = 89%

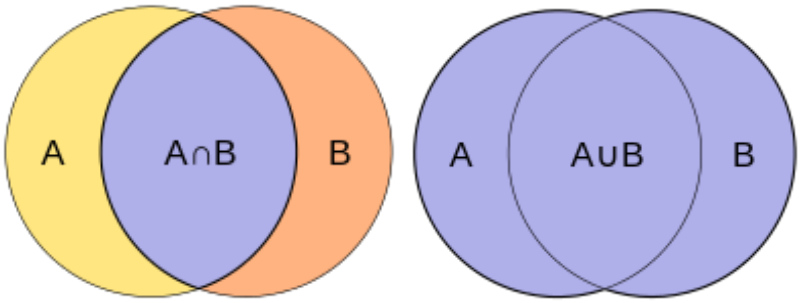
The NPV from this is : 70 / (70+75) = 81%

It can be inferred that when disease incidence is greater, the PPV tends to be greater while the NPV tends to be lower, and vice versa. Conclusions drawn using this approach should be taken cautiously(135).

- Another method for evaluating the classifier's output is to use the Receiver Operating Characteristic (ROC), which is often used in medical diagnostic evaluation. It shows how well the trial thing can discriminate between binary responses, such as how well a modern diagnostic approach can discriminate between cancer and the absence of cancer. For that reason, a cut-off point can be created. (135).

On the other hand, the Jaccard Index (or intersection of the union) can be used to evaluate the model's output by comparing the expected and actual patterns. It is equivalent to the number of intersections divided by the number of unions. The closer the model is to 1, the more similar the model and the reality are.

Figure 2.6 The Intersection (left) and the union (right, all blue)



For instance, the full circle of yellow indicates the quantity of actual data to be evaluated, which in this case is 90 samples. Then, the whole orange circle represents the data that was evaluated by the model, which is identical to the yellow number. The number of right cases estimated by the model is equal to the intersection A B. (in this example 80). Whereas A and B are the instances that the model does not right. If A equals 10, then B equals 10. Thus, A + (A B) + B = 100. The Jaccard Index would then be 80/100 = 0.8, closer to one. It indicates that the model's findings are identical to the real data by 0.8 (136). As the binary classifier can be converted to a 2x2 table, a chi-square test for homogeneity can be used to decide if the model produces identical results when applied to the actual data.

2.3 Application Programming Interface in Healthcare

Application programming interfaces (APIs) are essentially a method in which several inputs are given to a program to obtain the desired output. This requires the sharing of data and the understanding of such protocols by the machine. A common example is how to book accommodation online by inputting the desired date, type of accommodation, and other preferences into an application, which then returns the expected details. APIs perform a variety of functions in health care, including data exchange between health providers and other relevant offices, data aggregation, which is critical as a source of accurate information, especially when developing policy, and, most importantly, clinical decision making. The simplest method, for example, is provided by MDCalc, which makes clinical decision-making as easy as performing calculations on a calculator. Today, the artificial intelligence model can be incorporated into a single convenient framework through this API, implying that even the burden of clinical decision-making can be alleviated with the help of APIs (137).

CHAPTER 3

METHODOLOGY

1. STUDY CENTER

The research featured centers capable of managing drug-resistant tuberculosis, including diagnosis and treatment. A criterion for center selection was derived from Ministry of Health Regulation No. 67 of 2016 on tuberculosis management, which states that the research center should include the following:(138)

a. Capability to execute Ziehl Neelsen sputum smears.

b. Capacity to conduct rapid molecular diagnostic tests (GenXpert).

c. Capacity to administer a Drug Susceptibility Test.

d. Handle cases referred by other healthcare centers via TB.06 or MDR forms.

e. Access to chest X-ray examinations.

There were some additional criteria to select the center including the provision of standardized laboratory for the examination (such as NGSP/National Glycohemoglobin Standardization Program for HbA1c Assessment (139), Pulmonology Outpatient Department, Internal Medicine Outpatient Department, and appointed Tuberculosis Manager. Several hospitals that fulfilled the required criteria including :(140)

1. Central Laboratory Surabaya under the affiliation of dr Sutomo Hospital
2. The Microbiology Laboratory University of Indonesia, in conjunction with Persahabatan Hospital and Ciptomangunkusomo Hospital
3. Central Laboratory Bandung, associated with Hasan Sadikin Hospital
4. NHCR Makassar,integrated to Wahidin Sudiro Husodo General Hospital, and Hasanuddin University Hospital,
5. Semarang's Central Laboratory
6. Jayapura Central Laboratory

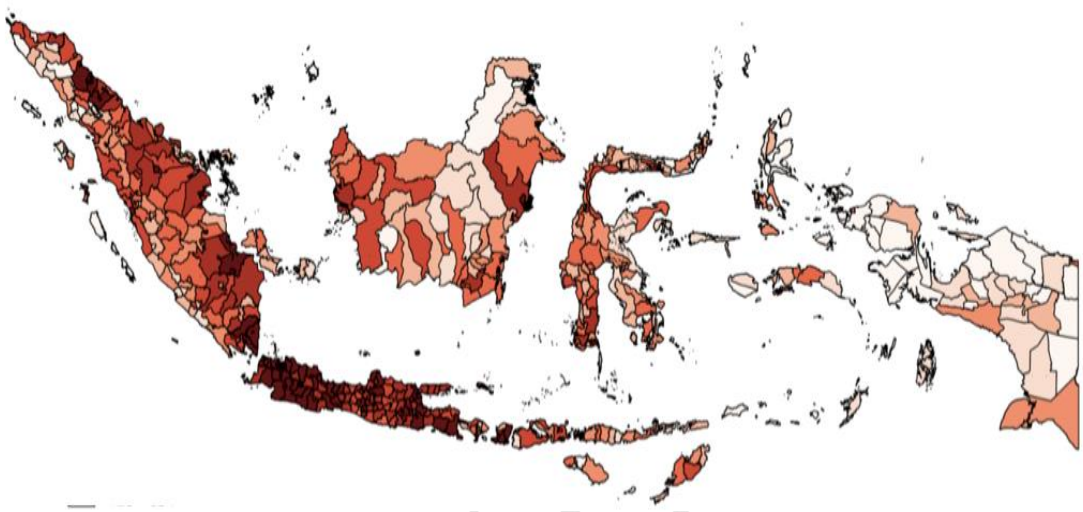
7. Microbiology Laboratory Gajah Mada University, in conjunction with dr Sardjito Hospital (unaccredited)

8. Adam Malik General Hospital Medan North Sumatera(unaccredited)

10. Central Laboratory Jakarta (unaccredited)

Further consideration was the high burden province of tuberculosis (above 20,000 cases) which were West Java, Central Java, East Java, North Sumatera, Banten, and South Sulawesi. The provinces with cases above 15,000 were South Sumatera and Lampung. (19)

Figure 3.1. Distribution of Tuberculosis In Indonesia as per January 2019



The North Sumatera and Central Java were excluded due to the KNCV's unaccredited laboratory status. A study of RR-TB was also conducted in West Java and Banten in the previous time, hence, to study in the same area would be redundant. The South Sulawesi Center represents not only South Sulawesi but also the neighboring provinces of Sulawesi Island and eastern Indonesia, making it a study center capable of accommodating a larger number of participants. In recognition of this, the recommended study locations were Jakarta, East Java, and South Sulawesi.

The researcher was considering the quality of the laboratories in these three centers as well as the COVID 19 situation. Jakarta and East Java were severely hit by COVID 19, thus impeded the research progress in these centers. The Research Center founded in South Sulawesi by the Novartis Institute for Tropical Diseases, the Eijkman

Institute, and Hasanuddin University focuses on tuberculosis and dengue, making it superior to other diseases. As a result, the investigator designated this study area as the primary research center. Additional study centers were requested specifically to conduct a validation procedure using prospective data, if possible. However, the final phase of this research did not require the inclusion of any additional centers.

Since the secondary data came from the hospital system's centralized medical records, access to the secondary data required ethical approval from the hospital's associated university. This letter then referred to the hospitals' Medical Education and Clinical Training unit. The chairman of this unit granted access to the medical records and electronic system on behalf of the hospital's director. Regular reports to the head of the medical record unit included the number of medical documents and details gathered. Appointed workers watched the researchers for a specified period to ensure that the medical records were not taken outside the office. Additionally, the researcher was instructed not to photograph any medical records. In the case of electronic medical records, the researcher requested the data based on eligibility requirements, which were obtained by workers. Normally, only those closely associated with the university are given a username and password to gain direct access to the data, but this was not the case in our situation. On data analysis and trial, assigned personnel from the study center assisted the data analysis monitoring.

The data were observed and tracked by personnel from the hospital's Medical Education Unit and Clinical Training, and the final data were transmitted electronically to the other investigators. The progress of the research, including data collection and analysis, was communicated to the host university's ethical committee. Moreover, the research centers required that the trial's final production (the application) be disseminated to health care providers following the trial's conclusion. Subsequently, the dataset was disseminated through a restricted/private online repository (with identifying information removed to ensure anonymity), allowing specific external parties, most notably the reviewer of a journal, to inspect the data's consistency and verify the reproducibility of the specified methodology.

2. STUDY POPULATION

The study population included individuals diagnosed with rifampicin resistance according to the guideline (this included polyresistant cases that included rifampicin resistance and multidrug-resistant individuals) and all

presumptive cases that underwent drug susceptibility testing. The gold standard for diagnosing drug resistance is the drug susceptibility test (141). The eligibility criteria were as follow:

1. Age above 15 years old

The minimum age for sputum testing and general reporting in the tuberculosis program has been recognized as 15. Under the age of 15, sputum analysis may not be optimal so additional attempts should be made to induce expectoration, such as nebulization with 3% saline, bronchial lavage, and any other methods that are expensive and inconvenient for the patient (142) (143). Tuberculosis in children often manifests in an unspecific manifestation (144) hence, the participants under the age of 15 years were omitted due to a possible technical problem.

2. Diagnosed as pulmonary tuberculosis (A15-A.16)

As tuberculosis is transmitted through the lungs, a strong emphasis was placed on this issue. Pulmonary tuberculosis can be usually observed using a sputum smear. and sample collection requires a noninvasive procedure, in contrast to the tuberculin skin test, IGRA, or any other test performed specifically for nonpulmonary tuberculosis(which accounts for a smaller proportion of cases than pulmonary tuberculosis). X-ray of the chest Examination can be used to validate the diagnosis since the chest X-ray of pulmonary tuberculosis demonstrates pathognomonic features such as convergence of the upper lobe of the lung, cavity formation, and classification. A team that confirms tuberculosis cases usually consists of a medical doctor, a radiologist, and a laboratory technician. (145)

3. Being referred to the study center to undergo drug-resistant testing.

All presumptive drug-resistant tuberculosis cases referred for testing using form TB 06 MDR and form TB 05 were included, including rapid diagnostic tests and drug susceptibility tests. The absence of details about the drug susceptibility test outcome before DR-TB treatment was the reason to exclude the participants. Presumptive cases are those that meet one of the following criteria:(146)

a. contact with a drug-resistant tuberculosis patient

b. tuberculosis case with failed or dropped out treatment, or relapsed

c. tuberculosis case with weakened immunity due to HIV, malignancy, chronic diseases such as prolonged and/or uncontrolled diabetes mellitus, or a history of substance abuse.

d. tuberculosis with physician consideration that this case is presumably resistant

4. Complete information on important variables.

All qualified participants with traceable information were included unless no traceable information was available via the medical record, tuberculosis form, electronic database, or clarification from the health center that refers to the cases.

3 STUDY DESIGN

This study applied various designs in multiple stages. Concerning the first and the second objective, the researcher implemented a cross-sectional design based on the data from January 2015-December 2019. This stage was purposively done for model building using the data from:

1. Medical records

2. National Tuberculosis Registration /TB Form

3. Electronic records from National Health Security Office

The next stage was developing the model and application using big data analysis. The model was tested with different data set yielded from January 2020-October 2020 and set as the core model to be embedded into the application.

A further qualitative study with in-depth interviews was conducted to assess the feasibility and the acceptability of the application by the healthcare staff in primary healthcare. This qualitative study was conducted according to the CHECKLIST OF THE QUALITATIVE RESEARCH (COREQ) (147)

A thematic analysis was preferred over content analysis to accommodate simultaneous manifest and latent analysis to obtain a deeper level of interpretation (148). Online invitation and snowball technique was used to recruit the participants with the objective of the study and procedure provided in the link. Participants were also encouraged to try the application with the DST-Confirmed cases at their workplace. An interview was conducted afterward through an online video meeting platform.

The major theme and interview guideline was derived from the MDR-TB mathematical dynamic model (149) and the healthcare service delivery model(150) to identify the true problem of DR-TB in the health care system. User experience assessment was analyzed based on the User Engagement Model to online intervention(151). Digital dictation using Indonesian Language recognition was applied to collect the transcript for further English translation. Data saturation was performed using inductive thematic saturation was conducted for data saturation,

Basic demographic information and user experience on a 10-Likert scale were collected as supporting data including the ease of use, clarity of information provided in the application, and feasibility of the application to be implemented at the participant's workplace.

The next study design was the cohort-selection cross-sectional study to answer the other objectives including the screening validation and cost-effectiveness of the model. The screening started from the suspected patients and these patients underwent two different screening methods using the GeneXpert and the Model. (152).

4 SAMPLE SIZE AND RECRUITMENT

The sample size calculation for the first stage was applied to yield the appropriate sample for model building. From the initial screening of 4142 retrospective data in the database, only 487 eligible participants can be analyzed. The prospectively collected data was 157 from 402 participants. This situation was heavily affected by COVID 19.

A calculation was made to justify whether the available data was sufficient enough. In the diagnostic study, a sample size calculation focused on the value of the screening/diagnosis including accuracy, sensitivity, and specificity. Furthermore, the prevalence of RR-TB was also essential.

As this study's objective is to build a screening tool, sensitivity was the important element for sample size calculation. The researcher took an estimated prevalence of RR-TB among suspected RR-TB is 10% from a study in West Java, Indonesia(153) However, the study was conducted in the hospital which then affects the real prevalence as hospitals tend to recruit a bigger number of sick people, therefore, the sample size calculation was solely dependent on sensitivity value. The researcher set a null hypothesis of 85% sensitivity (P0) and 90% as an alternative hypothesis (P1) (approximate power 90% (1-β) and type I error/α as 5%) which ended with a total of 471 participants (154) The hypothesis can be depicted as H0: Se = P0 versus H1: Se $\neq$ P0 (or Se = P1) with the formula as follows:

$$n = \frac{\left[Z\frac{\alpha}{2}\sqrt{P0(1-P0}+Z\beta\sqrt{P1(1-P1)}\right]^2}{(P1-P0)^2}$$

Research assistants were assigned to oversee data collection in each center. The research assistants received training in human basic research to ensure that data collection adheres to the procedure and ethical standards. Permission was granted for the research assistant to access medical records and laboratory registers at the centers, compiling all data into a single online submission machine. All data between January 2015 and December 2019 was collected to develop a model (stage one).

To validate the screening performance of the model in the second stage of the study and also for conducting the cost-effectiveness analysis, multiple prospective participants should be recruited based on a drug susceptibility test to compare the GeneXpert and the model performance using the study design below.

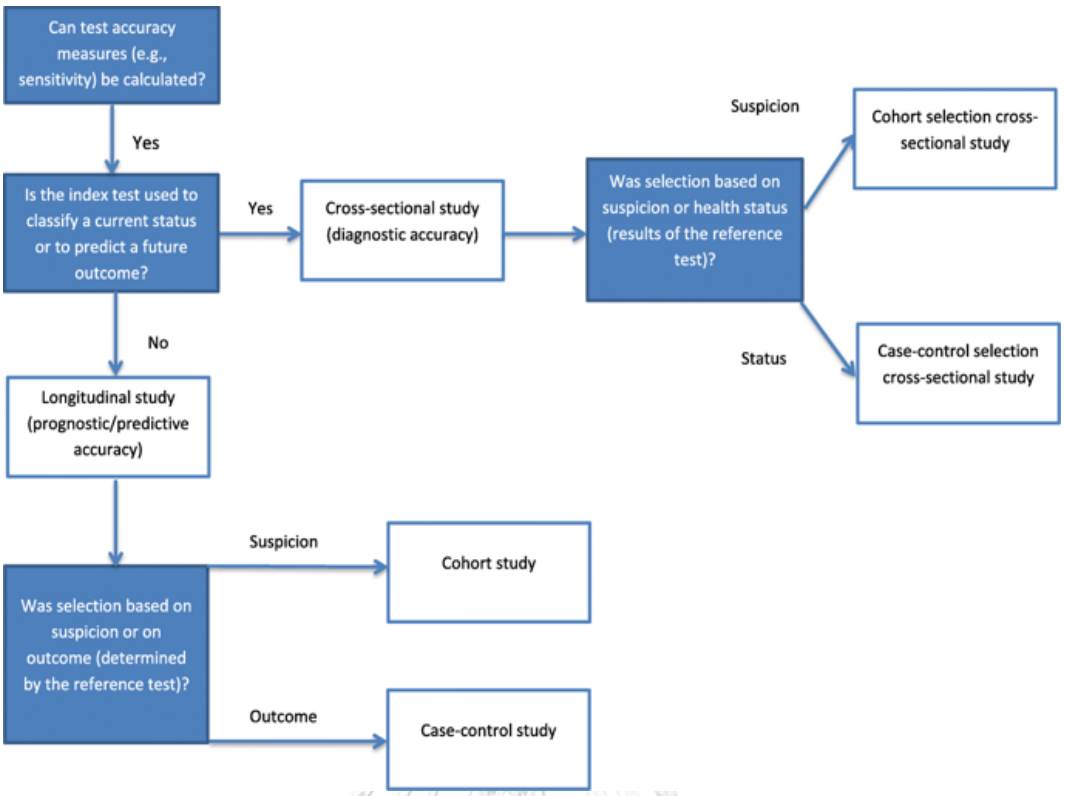


Figure 3.2. Pathway of Diagnostic Study Design

The diagram from Mathes (152) illustrates the process of performing the diagnostic performance assessment. The Artificial Neural network Model as the index test was then used to identify the current state and forecast future outcomes. A prospective sample of suspected patients was evaluated using the model and a reference test (culture/DST) to ascertain the disease's status; therefore, a cross-sectional cohort selection study was chosen.

According to a study conducted in Brazil, Artificial Intelligence using an Artificial Neural Network model has a sensitivity of 95% and specificity of 85% for differentiating drug-resistant tuberculosis from non-drug-resistant (155).

The sample size calculation was conducted for the second stage. Such modifications were contemplated using a 5% margin of error and a 95% confidence level. The researcher formulated a null hypothesis of 0.70 indicates the sensitivity of the model is 70%. An alternative hypothesis indicated that the model has a sensitivity of 0.90 or 90% and the power of study at least 80%. The prevalence was calculated as the number of positive rifampicin-resistant cases per 1,000 people tested, based on a study in West Java that accounted for 10% of the population. Using this

criterion, a minimum of 31 positive cases and 270 negative cases should be obtained, totaling 310 cases. This number is sufficient to demonstrate that the model has a sensitivity of between 70% and 90% and a specificity of between 90% and 95% (156)

The second stage was aimed to collect 310 prospective participants from January 2020 onward, however, the hospitals were in a hefty situation and the GeneXpert was allocated for COVID 19 testing, leading to early termination of prospective data collection in October 2020. Since the prospective case number for validation was smaller, the bootstrap method was implemented to yield more numbers with a similar confidence interval. The validation was done in two ways, using the initial 157 number and the bootstrapped number to overcome the small number of prospective participants. For the cost-effectiveness analysis, a total of the last 330 cases were included for the simulation of cost-effectiveness analysis.

5. VARIABLE OF INTERESTS AND MEASUREMENTS

Interest variables or parameters were divided into various categories based on their characteristics, which include the following:

5.1. Sociodemographic variables

a. Age was defined as the participants' age (in years) at the time of admission to the study center for drug-resistant evaluation. A continuous variable was collected and data discretization was used to regroup this variable with the cutoff of 40 years old. (157)

b. The term "gender" refers to the gender assigned at birth. A binary coding system was inferred, with the male was defined as 1 and the female defined as 0.

c. The education level was determined by the current educational system. From 0 to 5, the number 0 reflects illiteracy, 1 represents primary education, 2 represents secondary education, 3 represents diploma, bachelor's degrees, and postgraduate degrees.

d. Health Insurance was described as the possession of either national or private health insurance to cover medical expenses. For participants who do not have insurance, a value of 0 was assigned.

e. Marital Status was categorized as a binary answer, with 0 representing married or cohabiting couples and 1 representing single, divorced, or widowed individuals.

f. Employment status was described as having a job that provides for basic needs. Working participants were coded as 0, while unemployed participants were coded as 1.

These variables were accessed from the nurse's general assessment page, which was documented on each admission's medical record.

5.2. Host Immunity

These factors are associated with the state of immunity to eradicate foreign bodies and microorganisms. The following conditions can impair immunity:

a. Diabetes Mellitus

Diabetes mellitus has long been recognized as a risk factor for tuberculosis. Certain risk factors for diabetes include the duration of diagnosis with diabetes, the presence of complications, and glycemic control. A physician diagnoses diabetes mellitus as E.11 in the International Classification of Diseases 10 based on the American Diabetes Association guidelines attached in the appendix(158).

Diabetes duration was described as the period from diagnosis to admission to a center for drug-resistant assessment. Diabetic complications may include retinopathy, peripheral artery disease, diabetic neuropathy, or diabetic kidney disease. Good glycemic control is characterized as HbA1c levels reaching target therapy for no more than 6,5% on the day, or no more than three months before admission for drug-resistant evaluation. A binary response of 0 indicates that blood glucose was under control, while 1 indicates that blood glucose was not uncontrolled. To convert the value of random blood glucose to the HbA1c value, a conversion factor may be used from the capillary blood glucose value (159).

b. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) patients may present with similar clinical symptoms to tuberculosis patients, including chronic cough. To differentiate the disease, a respiratory function measurement using

respirometry was used to determine the percentage of forced expiratory volume in one second (FEV1). The classification of COPD was determined using the Global Initiative for Obstructive Lung Disease Classification/ Gold (see appendix). A participant with COPD (J.44 in ICD 10) was coded as 1 and without COPD was recorded as 0.

c. Body Mass Index (BMI)

The body mass index was specified as the weight of the subject in kilograms as determined by a spring balanced scale divided by the square of the subject's height in meters. The body mass index was measured as continuous data and discretized based on this classification of based on the Asian population.

Table.3.1 Classification of Body Mass Index

Score	Category	Code
Under 18.5	Underweight	5
18.5–22.9	normal weight	4
23–24.9	overweight	3
25-30	class I obesity	2
Above 30	class II obesity	1

The preceding code was organized following the finding that body mass index has an inverse relationship with sputum conversion time which contributes to drug resistance. (160)

d. Infected with the Human Immunodeficiency Virus (36)

For patients with HIV infection, the standard of the procedure is a quick anti-HIV test verified by ELISA at the hospital level to quantify the antibody level. This test would be performed on all tuberculosis patients who were presumed to be drug-resistant. A binary code of 0 indicates that the sample was non-reactive, while a binary code of 1 indicates that the sample was reactive or that HIV was present. The ICD 10 code B.20 denotes patients who have HIV

e. Smoking

As with body mass index, smoking may prolong the time required for sputum conversion, as demonstrated by a Japanese study (161). Brinkman's index was used to classify the magnitude of the smoking habit as quoted in

Watanabe. (162) by multiplying the daily amount of cigarettes smoked by the number of years smoked. Continuous data was obtained and discretized using a value of 600, which was considered to be a heavy smoker.

f. Alcohol consumption

Despite Indonesia's conservative stance on alcohol, alcohol use is still prevalent in some areas. Only recent alcohol intake during the last six months or prior to tuberculosis treatment was coded as 1 and vice versa.

g. Immunosuppressive agent

Any history of extended immunosuppressive agent use, including glucocorticoids (for more than 3 weeks) should be reported (104) as it impairs host immunity by altering immune function and cell differentiation (103). Since immunosuppressive agents used to treat cancer, such as tacrolimus, can have an immediate impact, short-term use was reported regardless of the duration (163). Any history of use of these immunosuppressive agents that meet the requirements outlined above coded as 1

h. History of Drug Abuse

Any history of injectable morphine use or drug misuse, including alcohol, amphetamine, or illicit substances, was classified as 1

i. History of adverse tuberculosis drug reaction

The adverse reaction to previous tuberculosis treatment, particularly the extreme type, which included drug-induced hepatitis, ototoxicity, and severe neuropathy, compelled the physician to change the tuberculosis regimen, which may be less effective than normal. (57) This occurrence can also have an impact on treatment adherence, resulting in dropouts or unresolved cases. Any history of an adverse tuberculosis drug reaction is typically reported in the drug reaction type, and for the study, this occurrence was assigned a value of 1, whereas no history of an adverse tuberculosis drug reaction was assigned a value of 0

j. Adherence to previous tuberculosis treatment.

The Directly Observed Care Shortcourse/DOTS is a program that monitors compliance with tuberculosis treatment guidelines. One component is including the community health care provider and the patient's family in monitoring medication adherence. Any instances of therapy non-compliance will be identified, and additional evaluation, especially of drug-resistant patients, will be performed. Each participant who adheres fully or has never been treated previously for tuberculosis (in primary drug-resistant infection) was assigned a score of 0, while any participant who demonstrated non-adherence to therapy was assigned a score of 1.

k. Presence of Chronic Disease

Any other chronic condition, such as stroke, heart disease, mental illness, or any other disease requiring long-term management and therapy, was classified as 1

5.3 Manifestation of Agent

While molecular epidemiology has successfully established many tuberculosis strains that are resistant to treatment(164) since the aim of this study was to construct a model using variables obtained from clinical practice, the method used to classify the strain and incorporate it into the model might affect the model's feasibility in a clinical environment. Clinical manifestations are the most accurate predictors of an agent's virulence and effect on the host. These variables include the following:

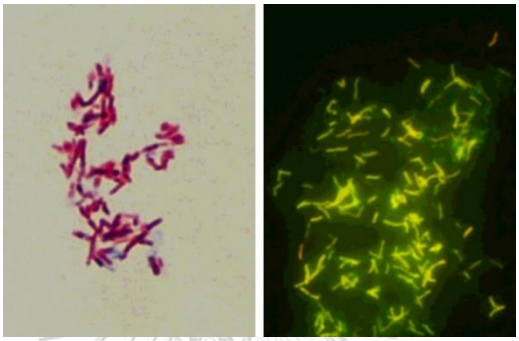
a. Level of sputum smear

The bacillary index was determined prior to the start of treatment in this analysis. A formula has been developed to calculate the bacillary index based on microscopic findings (38) :

- Negative : No acid-fast stained bacteria observed in 100 fields
- Scanty : 1-9 acid-fast bacteria observed in 100 fields
- 1+ : 10-99 acid-fast bacteria observed in 100 fields
- 2+ : 1-10 acid-fast bacteria per field observed in 50 fields
- 3+ : > 10 acid-fast per field bacteria observed in 20 fields

Although another sputum smear technique using the fluorescent method is possible, it is uncommon to use in clinical settings, especially those with limited resources. A serial code ranging from 0 to 4 was assigned to each sputum smear stage.

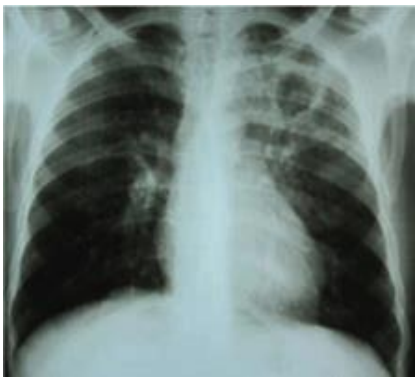
Figure 3.3 Sputum Smear more than 10 bacteria per field (red) stacked above the non-tuberculous bacteria (blue) and fluorescent mode (green) (165)



b. Extension of Lesion in Radiology Examination and Presence of Cavities

Following the analysis of the literature, the radiology evaluation would be based on a chest X-ray or chest CT scan. To accomplish the study's objective, the radiographic presence of the lung was divided into three parts (upper, middle, and lower) per lung, totaling six sections. Cavity, Gohn Emphasis, consolidation, hilar lymphadenopathy, milliary presentation, or pleural effusion were all specific findings of active tuberculosis in this study (166). Any signs of this in one section were considered as one section, two findings in two different sections, the extension of the lesion were two sections until maximum 6 section. The presence of the cavity was defined as yes (1) or no (2) and a number of the cavity was also observed.

Figure 3.4. Chest X-Ray with a cavity at the upper right lung (166)



5.4 Environment Factor

Mycobacterium's ability to remain viable in an air droplet is supported by optimal conditions, which means that environmental factors play a role in tuberculosis transmission.

a. History of contact with a tuberculosis patient

Tuberculosis is transmitted by inhalation of an air droplet containing Mycobacterium tuberculosis, but symptoms may not manifest until the immune system is compromised. This is referred to as latent infection. An individual may develop primary drug-resistant tuberculosis if they have no prior tuberculosis infection, which may occur as a result of interaction with a positive drug-resistant case, while a secondary drug-resistant tuberculosis case is followed by an unresolved primary tuberculosis case(34). Any cases with a history of contact with tuberculosis patients were coded as 1.

5.5 Access to the data

As discussed previously, data collection was primarily based on medical records, whether in hard copy or electronic format. Access to this data was provided with the center's permission, and the investigator should protect the data's confidentiality.

a. Medical Record: The initial evaluation form contains information about the patient's sociodemographic characteristics, disease history, and analysis. Hospitals accredited by the National and Joint Commission International attest to the accuracy of this information.

b. Tuberculosis National Registration Form (The Multi-Drug-resistant format). Tuberculosis Manager manages these types, which include details about sputum smear results, rapid diagnostic test results, drug susceptibility test (TB05), and other data (including sociodemographic data)(167) :

1. List suspected cases with smear sputum (TB06)

2. Sputum Smear Request Form (contains information) regarding sputum smear, rapid diagnostic test results, drug susceptibility test (TB05)

3. Treatment Card (TB01)

4. Tuberculosis Identity Card (TB02)

5. Referral Form (TB09)

6. Laboratory Register (TB04)

c. For those who have national health insurance, personal electronic records from Badan Penyelenggara Jaminan Sosial Kesehatan (National Health Security Office) include details such as individual laboratory screening for productive age (blood glucose, lipid profile, liver function, kidney function, and other screening) and a history of a visit to a primary care center. This was accessible upon formal request. Each page contains unique information based on the user's national identification number.

6 ARTIFICIAL NEURAL NETWORK BUILDING

The Neural Network is structured similarly to human neuron cells, with many interconnected processing nodes connected by weighted connections. The training algorithm changes the relation weights iteratively to minimize error. (168)

These were the steps to build an artificial neural network in this study:

a. Determine the general structure (radial basis function (RBF) or multi-layer perceptron (MLP).

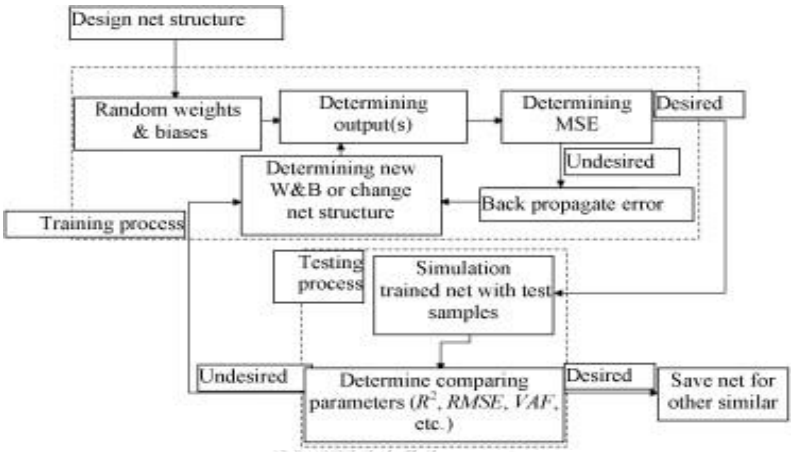
b. Determine parameters

c. Cleaning and managing data (imbalanced data, discretization, normalization)

d. Hyperparameter tuning

e. Model Selection and Validation

Figure 3.5. General Procedure of Artificial Neural Network (169)



6.1 General Structure and Steps

There were two general structures were considered in this study which were the radial basis function (RBF) and multi-layer perceptron (MLP). A study exhibited a superiority of the Radial Basis Function over the Multilayer perceptron (MLP) to predict continuous outcomes (170). Furthermore, another evidence of the model to screen diabetes with Radial Basis Function had better accuracy (171). However, concerning the complex parameter and interconnection, this study preferred the multi-layer perceptron (MLP).

6.2 Determine Parameter

There are many types of parameters in predictors, the majority of which are binary responses. Combining these parameters results in the development of hundreds of models; thus, consideration should be given to which parameters should be entered. What were the component selection strategies?

a. Model with All Parameters

This was called the full model. A data cleaning process was applied to sort all cases and ensure that all parameters to be used in the model have complete details. The downside of this method was that it reduced the number of cases to train and the size of the test (listwise deletion).

c. Bivariate model

The model was built solely based on the related predictors from the bivariate analysis using the chi-square or the correlation box plot

d. Short model

The model was considered based on a parameter that demonstrates causality and plausibility to the RR-TB as determined by a supporting literature review or proof, and also with very minimal risk of recall bias such as data from laboratory examination,

6.3 Insufficient and Imbalanced data class

Due to the bias introduced by imbalanced data, which causes the model to expect the majority response (127), a setting data ratio of 1:1 (positive: negative) was planned to determine the proportion of data to use in training and test data. This was the optimal way to avoid a model of low precision. However, the ratio of positive to negative was asymmetric. The technique at the data level can be used. In this case, the data initially built with the proportion of 1:9 and 1:1according to West Java prevalence, where for every ten presumptive cases of drug resistance, one case is true RR-TB positive (153). However, the true prevalence of this study was somewhat higher and there was an attempt to reach a balanced proportion by retrieving more data but the last COVID 19 circumstances affected further data collection.

In the situation of data imbalance, there was a term to be considered which were the words "oversampled" or "undersampled". By looking at the collected data where positive cases were seemingly lower than the negative case, the positive case needed to oversample, or the negative cases should be undersampled to achieve the balance proportion. The investigator was planned to apply The Synthetic Minority Over-Sampling Technique (SMOTE). A combination of these factors may result in an improved model. (172). However, by looking at limited eligible data and possible data size reduction, this procedure was not implemented, and the researcher went with the initial true proportion from the data.

6.4 Normalization

Normalization in a neural network is not the same as in general data distribution. It is not an attempt to normalize the data, but rather a conversion of the values of a particular numeric parameter to a common scale, without distorting the range of values or obliterating any information. This is done to ensure that the input and output

parameters have a similar set of values. Normalization techniques include Average, Decimal scaling, Mean-Man, Median-Mad, Min-Max, and Z-score(173) and their application is dependent on the type of data.

This normalization would aid in the acceleration of the neural network train. Although the majority of the parameters have a binary or ordinal answer, some variables, such as age, have a broad range of interval values. If the means of all data parameters are close to zero or have a similar interval, normalization is possible. A discretization technique will be used to group certain continuous data with a wider range of values, such as age. If this is not possible, a min-max normalization approach is preferable. (174). Batch normalization may sometimes be used to change and scale the activation nodes in - layer, thus compensating for the internal covariance shift. This also mitigates the risk of overfitting. (175). In this study, the discretization was performed to ease the normalization process and further step using the min-max normalization was applied to normalize the input or the general structure.

6.5 Hyperparameter setting and Optimization

The artificial neural network command was used in the R program as “neuralnet” with the following setting,

- Number of Hidden Layers

  A sequential method was conducted in this study by adding the hidden layer sequentially. The final model had two hidden layers.

- Dropout of neurons

  A probability value of the input and output nodes was used to drop out some neurons. A 0.5 value was set for this purpose.

- Activation function

  A combination of the sigmoid in the hidden layer and the sigmoid in the output nodes was applied as an activation function.

- Weight Initialization

  Multiple weight initialization was conducted, with random initialization.

- Iteration

  Ranging from 10000-100000 steps and automatically stop when convergence was reached.

- Training and Test Data Distribution

  A proportion of 85:15 of data was used for training: test data and split manually

- Threshold

  A 0.01 manual threshold was set.

- Repetition

  Ranging from 10-20 times

6.6 Model Selection and Validation

The models were evaluated based on the Area Under Curve (AUC), Accuracy, Sensitivity, Specificity, and Log loss Cross-Entropy of the models according to the testing data. A cutoff of 0.5 likelihood for the result interpretation. A total of six ANN models were developed and saved as .rds file.

6.7 Development of other classifiers

The researcher developed four distinct categories of classifiers: Decision Trees (DT), Random Forests (RF), Logistic Regression (LR), and Extreme Gradient Boosting (EGB) (XGB). The data splitting ratio of 85:15 was used. The optimal model for both LR and DT was determined using the sensitivity value of the testing results. For the RF and XGB models, the model with the lowest error after fivefold cross-validation was chosen as the best. There were a total of 12 models constructed(176)

7. OUTCOMES

7.1 Pulmonary Rifampicin Resistant Tuberculosis.

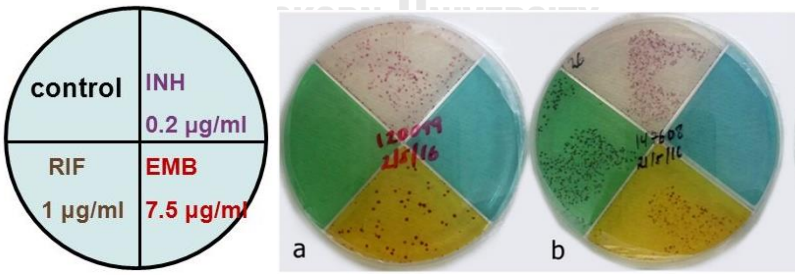
Technically, drug susceptibility is determined by comparing macroscopic growth in drug-containing (such as rifampicin) and drug-free media, detection and/or quantification of bacteria' metabolic activity or products, lysis content with mycobacteriophage; and 4) detection of genetic mutations using molecular methods (177). If any of the four conditions above are met, the client is positively diagnosed as rifampicin-resistant. This disorder is then coded as ICD 10 Cases of A.15 and A.16 with a minimum of U.50.0; U50.2-4 followed by background and physical inspection. In Indonesia, the following processes are implemented in drug-resistant cases:

a. Drug Susceptibility Test (DST)

The Drug Susceptibility Test (DST) is a method for determining a drug's ability to inhibit the growth of microorganisms in culture. Although the Löwenstein–Jensen medium has been recognized as the gold standard for Drug Susceptibility Testing (DST), other media such as BACTEC are also accessible. The proportional method, the absolute concentration method, and the resistant ratio method are commonly used to quantify performance. (178)

The proportion process, specified as the growth/number of colonies in the drug-containing medium divided by the growth of bacteria in the drug-free control medium and expressed as a percentage, was used to compare prospective participants' diagnostic results. Typically, the medium contains rifampicin (RIF), isoniazid (103), and Ethambutol (73) all of which are segregated into quartal zones. If the percentage exceeds 1%, resistance is present (178) The sputum was handled according to normal procedures and the DST method was used. Two samples of the morning and random sputum were digested and concentrated with N-acetyl-L-cysteine and sodium hydroxide. A 0.2 ml suspension was embedded in the LJ medium and observed weekly for growth. As shown in the figure below, plate A shows bacteria growing on a rifampicin plate (yellow plate), indicating that case A is Rifampicin Resistant, while plate B shows bacteria growing on isoniazid (green plate) and rifampicin plates. Plate B indicates a case of Multi-Drug Resistance (179)

Figure 3.6. The proportion method scheme with the drug-free zone and drug zone and growth on medium



The study center did not implement other methods than the proportion method. Another technique is to use the resistance ratio process, which is based on determining the sample's minimum inhibitory concentration concerning a normal laboratory strain (H37Rv). This approach introduces bias since the inoculum size and viability of the comparator strain were the primary determinants of the performance. The absolute concentration approach

employs a standardized inoculum grown on both drug-free and drug-containing media. The primary difficulty with this approach is ensuring the organism's viability; hence, the inoculum must be standardized appropriately. By means, the proportional methods have been chosen to determine drug resistance. (178). Apart from monitoring the bacteria's development, another way to determine is to measure their metabolic activity, which provides results in a short period. The BACTEC 460 can be used to detect CO2 output or to determine the amount of oxygen consumed by mycobacterium using the Mycobacteria Growth Indicator Tube. Immunoassays may also be used to detect some mycobacteria multiplication, even at very low levels. Nonetheless, due to the high cost, this device is rarely used in clinical settings. (177)

The latter new methods were recently introduced in the study center. To reduce the heterogeneity of the culture results, this study only recruited the participants that were tested with the proportion method.

b. Rapid Molecular Test :

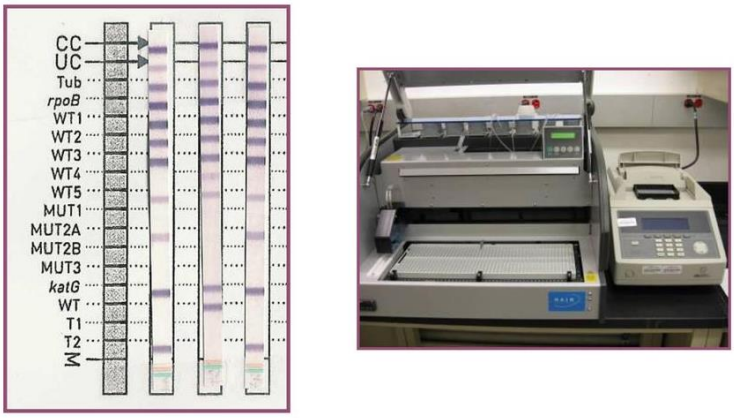
The GeneXpert is a cartridge-based nucleic acid amplification test (NAAT) designed to perform rapid tuberculosis diagnosis and antibiotic susceptibility testing concurrently. This was accomplished by combining the reagent for sample preparation with the sputum. This mixture was then agitated and incubated for 15 minutes at room temperature before being shaken again. The test cartridge was then filled with 2-3 ml of the mixture. Automatically, a corresponding procedure was loaded. The findings indicate the presence of Mycobacterium and Rifampicin Resistant Mycobacterium. This test is not a substitute for the gold standard, the Drug Susceptibility Test. (180) The common procedure in the study center was all presumptive drug-resistant tuberculosis was initially tested with GeneXpert with three possible outcomes, negative, intermediate, and positive. However, the GeneXpert was allocated for COVID testing which affects the collection of prospective patients.

Figure 3.7. GeneXpert (165)

c. Genotype

Another way to diagnose drug-resistant tuberculosis is to classify the drug-resistant gene. In the drug-resistant case, a mutation in the RNA Polymerase B subunit gene, or rpoB, was identified that specifies codons 507-533. This mutation renders rifampicin incapable of inhibiting RNA transcription. The Polymerase Chain Reaction (PCR) can be used to determine whether this gene has been mutated. This method was used as a last resort if the results of the previous procedure are unsatisfactory (28). For complicated cases, several participants were confirmed using this method and underwent final DST before treatment initiation.

Figure 3.8. Genotyping results showing positive for rpoB and katG, Indicating an MDR TB.



7.2 Screening Performance Assessment of the model

A confusion matrix was constructed to test the result yielded by the model and the confirmed-DST results using a 2 x 2 table derived from the function in R Program.

Table 3.4. A 2x2 Confusion Matrix

Model	Gold Standard (DST)	
	RR	No RR
Rifampicin Resistant (RR) Predicted Yes	A	B
Rifampicin Resistant (RR) Predicted No	C	D

A batch testing was implemented for all models with the prospective data. Further assessment with bootstrap data was conducted.

7.3 Cost-Effectiveness Analysis

As 330 participants were included for the cost analysis using medical billing. The purpose of cost analysis is to compare the model with the existing GeneXpert using the Drug Susceptibility Test as the gold standard. The cost-effectiveness analysis element was basically on the direct spending of the health care provider including :

a. Cost of GeneXpert

b. Cost of DST

c. Cost of Model

d. Miscellaneous costs

The Quality Adjusted Life Years/QALYs of untreated tuberculosis was used as the approximation of QALYs if the diagnosis is delayed.

The decision tree analysis was used, accommodating several assumptions including the prevalence of RR-TB among suspected cases, sensitivity of the model, sensitivity of the GeneXpert, cost per positive cases by GeneXpert and by Model, cost of negative cases by GeneXpert and by Model and the last line was the cost for DST for final confirmation. This yielded eight different scenarios

The Incremental Cost-Effectiveness Ratio will be calculated using this formula :

$$ICER\ Model = \frac{\text{Costs Model} - \text{Costs culture}}{Incremental\ QALYs}$$

and

$$ICER\ Xpert = \frac{\text{Costs Xpert} - \text{Costs culture}}{Incremental\ QALYs}$$

There were three different ICER values in this study. The ICER value of QALYs gained per prevented mortality, per prevented acute morbidity (such as symptoms that appear during the acute phase including shortness

of breath, fever, acute malnutrition), and per prevented chronic morbidity (Post TB obstructive syndrome, restlessness, etc).

Both ICER values compared Model and GeneXpert to yield the most efficient method in comparison with the gold standard on the same person. The sensitivity analysis was conducted to see the differences of ICER values in different prevalence and different sensitivity of the model.

8. ETHICAL PROCEDURE AND DATA PROTECTION

The Helsinki Declaration states that all reasonable measures must be taken to safeguard the privacy of research subjects and the confidentiality of their personal information (verse 24). As such, the investigator and sub-investigator have been provided basic ethical training about human subject safety before the Institutional Review Board (IRB) evaluation, as this analysis used medical records and electronic records that contain confidential information. The National Board of Research Indonesia was contacted to obtain a foreign research permit. A request for IRB approval was made to all collaborator centers and institutions (Hasanuddin University) as well as the host university (Chulalongkorn University). Additionally, this report was registered at www.clinicaltrials.gov (NCT04208789) to obtain the Number of Clinical Trials and to ensure the study's transparency and accountability. The data were checked by the host university's data monitoring team to ensure that no violations of the protocol or ethical procedures occur. The progress of the research was communicated to the host and collaborators, as well as posted to www.clinicaltrials.gov. As part of the accountability process, the study's findings were presented and published in a journal. The host university was financing this research under the 90th Anniversary Chulalongkorn University Ratchadapisek Endowment Fund.

CHAPTER 4

RESULTS

1. MODEL BUILDING

At an earlier stage, a total of 4142 potential subjects were filtered using the ICD code. By conducting a screening with the eligibility criteria, a total of 487 data were recruited in data building comprised of 89 subjects of DR-TB with rifampicin-resistant (32 subjects with MDR-TB) and 398 subjects with drug-sensitive TB. Several participants were excluded mainly due to incomplete information as demonstrated by figure 4.1. This study also screened three isoniazid-resistant but subsequently omitted them as the data of these subjects were incomplete. The treatment received by the subjects was the combination of Streptomycin + Levofloxacin + Ethambutol, following the issuance DST result. Table 4.1 elaborate the general characteristic of the subjects in the model building.

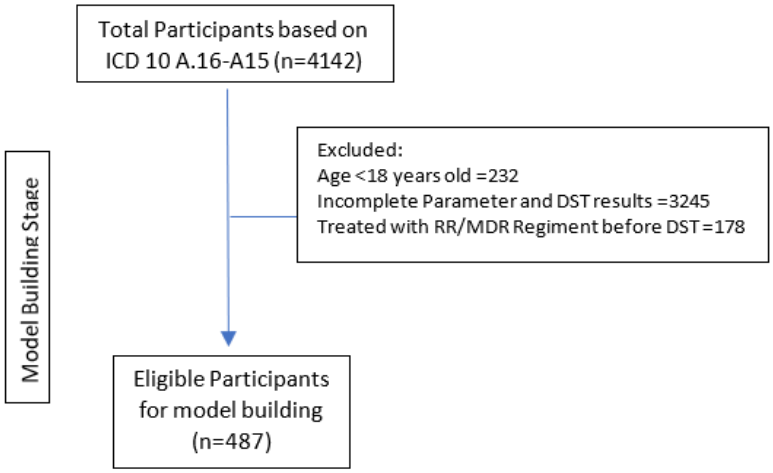


Figure 4.1 Participant flowchart of the model building

A total of 20 variables are listed in the table below with the bivariate analysis results of each variable, concerning the drug-resistant status. Among the 20 variables, 14 variables showed association with drug resistance. Non RR/MDR TB subjects tend to be younger. Diabetes mellitus, as well as the HbA1c value, are significant with the RR/MDR-TB. And among people with a previous history of TB treatment (n=161), there is a significant association between the adherence of previous TB treatment and the occurrence of RR/MDR-TB.

Table 4.1. Participant's characteristic in model building data (n=487)

Variable	Subset	RR + MDR (n=89)	Non-RR (n=398)	p value
Gender	Male	41	132	0.021
	Female	48	266	
Age (year)	<40	30	210	0.001
	40 and above	59	188	
	Mean ± SD	44.06 ± 11.57	39.59 ± 13.84	
Education	Illiterate	4	13	0.662[&]
	Primary Education	19	95	
	Secondary Education	64	271	
	College degree and above	2	19	
Universal Health Coverage	Covered	70	331	0.313
	Uncovered	19	67	
Current Employment Status	Employed	34	168	0.488
	unemployed	55	230	
History of Drug Abuse	Never	87	396	0.154[&]
	Yes	2	2	
Contact with positive DR-TB case	Never	61	381	<0.001
	Yes	28	17	
DM status	No	40	252	0.001
	Yes	49	146	0.004#
	Mean ± SD of HbA1c	7.33 ± 1.86	6.91 ± 1.95	
History of Previous TB treatment	Never	27	299	<0.001
	Yes	62	99	
HIV status	Reactive	26	77	0.039
	Non-Reactive	63	321	
Brinkmann Index	Never Smoke	53	340	<0.001
	1-600	27	55	
	>600	9	3	
Drink alcohol within one year	Never	86	395	0.078[&]
	yes	3	3	
Immunosuppressants use > 6 weeks	Never	85	390	0.245[&]
	Yes	4	8	
Number of Chronic Disease	Median ± IQR	0 ± 0	0 ± 0	<0.001^
	Min-Max	0-2	0-2	
Body Mass Index (kg/m2)	<18.5	49	74	<0.001
	18-5-<23	28	194	
	23-25	6	71	
	>25	6	59	
Adherence to Previous TB treatment	Yes	30	84	<0.001
	No	32	15	
Diagnosed as COPD	Yes	21	40	<0.001
	No	68	358	
Sputum Smear level	Negative or Scanty	3	285	
	1+	37	99	
	2+	32	9	<0.001
	3+	17	5	
Presence of Cavitation	Yes	55	77	
	No	34	321	<0.001
	Median Number ± IQR	0 ± 2	0 ± 0	<0.001[$]
	Min-Max of Cavitation	0-4	0-4	
Extension of Lesion	Median ± IQR	3 ± 1	2 ± 2	<0.001^
	Min-Max	1-4	0-4	

Abbreviation: COPD (Chronic Obstructive Pulmonary Disease), DM (Diabetes Mellitus), DR TB (Drug-Resistant Tuberculosis). DST (Drug Susceptibility Test), HbA1c (Hemoglobin Glycated 1c) HIV (Human Immunodeficiency Virus), IQR (Interquartile Range), Max (Maximum), MDR (multidrug-resistant) Min (Minimum), SD (Standard Deviation). All tested with Chi-Square, except (& = Fisher Exact). # is a Mann-Whitney U test for the difference between HbA1c values. $ is a Mann Whitney test for difference of cavitation number between the group, ^ tested with Mann Whitney. The baseline for prospective testing data provides as supplement table 1 (S1. Table and Equation)

Further analysis with the correlation plot was made to depict the bivariate association between all variables. Several associations between independent variables were also addressed including a positive correlation of Brinkmann index and COPD (0.63), and smear level with the DST result (0.64) which become the most significant predictor for DST result, as shown by this figure below.

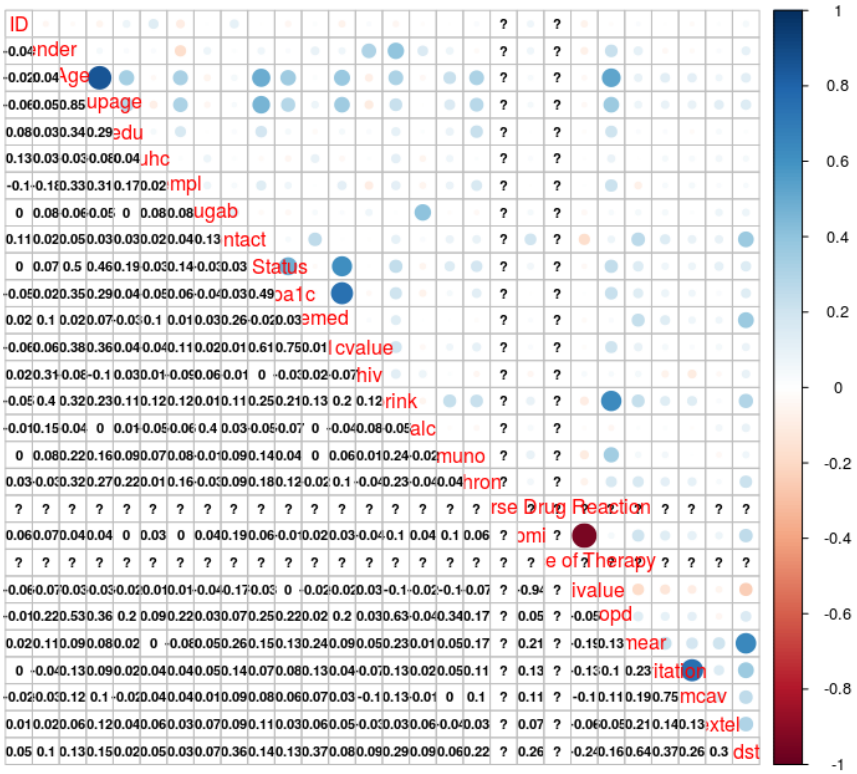


Figure 4.2 Correlation plot of all variables.

An “importance analysis” was conducted before developing the extreme gradient boost models (XGB). In the bivariate model, the most important factor is smear level (figure 4.3), whereas, in the full and short model, the extension of lesion and body mass index are important (appendix), as shown by the figures below

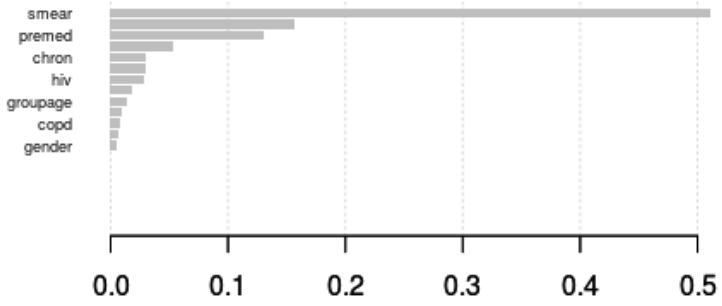


Figure 4.3 The importance analysis of variables in the bivariate model

The model building was conducted with the initial assessment of the sample whether it reaches convergence in the learning curve or not. Figure 4.2 Training size according to ROC value showing a convergence of training and testing data at more than 400 training data. Therefore, this data is sufficient for model building.

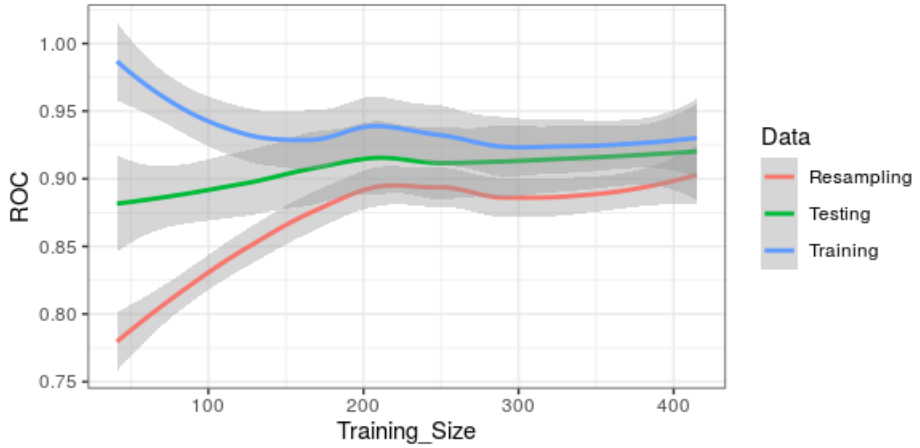


Figure 4.4 Convergence of data and ROC value

A total of six Artificial Neural Network was built with the following structure. Three groups of models were created based on the variable. The adherence to previous TB treatment was excluded as integrating this parameter resulted in a lower number of subjects for the model due to the listwise deletion. Those three models are the full model (which consists of 19 variables), the short model (8 variables), and the bivariate model (13 variables).

Table 4.2. Model of Artificial Neural Network

Model	Predictor	Hidden Layer 1	Hidden Layer 2	Maximum Steps	Repetition
ANN Full Model 2-1	19	2 Nodes	1 Node	100000	20
ANN Full Model 2-2	19	2 Nodes	2 Nodes	100000	20
ANN Short Model 2-1	8	2 Nodes	1 Node	1000000	10
ANN Short Model 2-2	8	2 Nodes	2 Nodes	1000000	10
ANN Bivariate Model 2-2	13	2 Nodes	2 Nodes	100000	20
ANN Bivariate Model 2-1	13	2 Nodes	1 Nodes	1000000	10
Footnote: set seed (123); Normalization with min-max; Train/Test = 85%:15% train-test split applied; training using neuralnet (resilient backpropagation); default threshold 0.01; activation function: Logistic; Loss: Cross Entropy					

Several models were also developed as comparators using the same dataset. A total of 12 models with four types of classifiers were created with the specific protocol mentioned in the table below.

Table 4.3 Model structure of other classifiers.

Model	Predictor	General Protocol
Logistic Regression 1	19	Function: glm.fit, Family binomial, Calculating LogLoss using Cross-Entropy
Logistic Regression 2	8	
Logistic Regression 3	13	
Extreme Gradient Boost 1	19	Function= xgboost. Using one hot encoding for creating dummy variables. Parameters consist of gbtree booster with eta = 0.3, no gamma regularization with a maximum depth of tree = 6, number of rounds = 100 with 5 cross-validations, and early stopping rounds function. The selection was based on the least error.
Extreme Gradient Boost 2	8	
Extreme Gradient Boost 3	13	
Decision Tree 1	19	Function: rpart, method=class. Accuracy tuning with rpart. control was prepared with minimum observation to exist in the node=4, with complexity parameter=0
Decision Tree 2	8	
Decision Tree 3	13	
Random Forest 1	19	Function= randomforest. Tuning parameter= mtry. Crossvalidation=5
Random Forest 2	8	
Random Forest 3	13	
Common protocol: seed before data splitting 123. 85%:15% train:test splitting		

The next section is the assessment of the model with a 15% dataset called test data. A total of 73 data was extracted from the dataset. The performance of the models comprised of sensitivity, specificity, log loss, the area under the curve, and accuracy.

Table 4.4 Performance of Artificial Neural Network model with 15% training data (N=73)

Model	TN	TP	FP	FN	%Acc (95% CI)	% Sens (95% CI)	% Spec (95% CI)	LogLoss	AUC
2.2 Full	51	16	3	3	92 (83-97)	84 (60-97)	94 (85-99)	1.53	0.96
2.1 Full	51	13	3	6	88 (78-94)	68 (43-87)	94 (85-99)	1.56	0.94
2.1 Short	52	13	2	6	89 (79-95)	68 (43-87)	96 (87-99)	0.91	0.95
2.2 Short	54	16	0	3	96 (88-99)	84 (60-97)	100 (93-100)	0.18	0.99
Bivariate 2-2	50	16	4	3	90(81-96)	84 (60-97)	93(82-98)	2.81	0.96
Bivariate 2-1	51	16	3	3	92(83-97)	84 (60-97)	94 (85-99)	1.25	0.98

Abbreviation: Acc = Accuracy; AUC = Area Under Curve; CI = Confidence Interval; FN = False Negative; FP = False Positive; TN = True Negative; TP = True Positive

As seen in table 4.4 the highest accuracy is shown by the short variable with two hidden layers with two hidden nodes in each layer. This model shows the highest specificity among all ANN models. The highest sensitivity is 84% and is seen in four models. The smallest log loss entropy and highest AUC are also shown by the short model with a 2-2 structure.

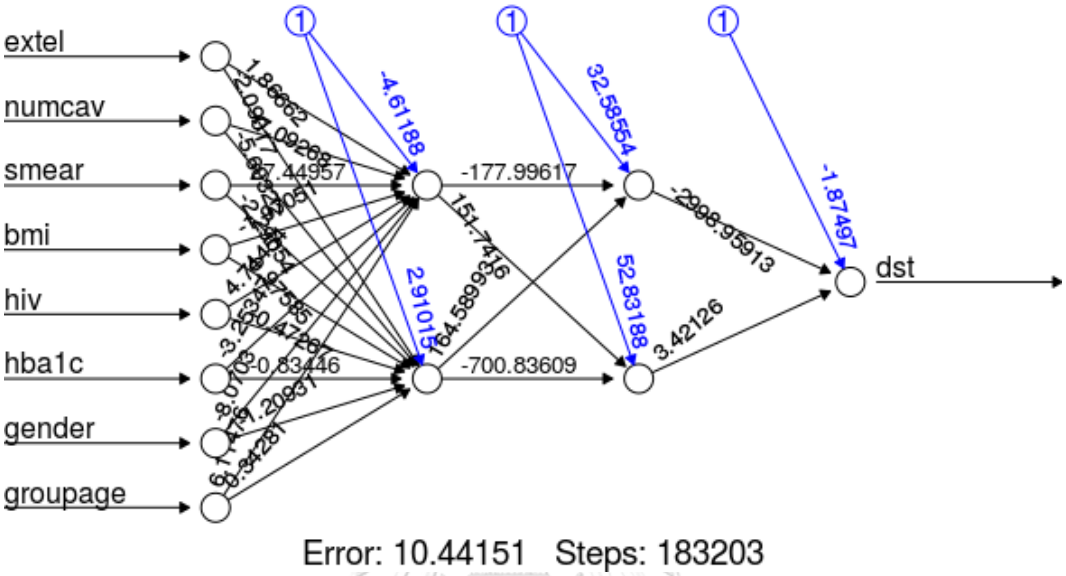


Figure 4.5 Structure of the ANN model short 2-2

The figure above illustrates the structure of the ANN model with two hidden layers and two nodes in each layer. The bias nodes are shown by the blue line with their weight. The model stopped learning at 183203 steps with the least error achieved 10.44151. The model used eight information including the number of extensions of the lesion, number of cavities, smear level, body mass index, HIV status, Hba1c level with the cutoff of 6.5, gender, and groupage with cut off 40 years old. Other model structures were shown in the appendix.

Twelve other models from four classifiers were also tested with the remaining 15% of data and the aforementioned algorithm. Several model structures were created. In the decision tree models, the initial nodes are the smear level followed by the number of extensions of the lesion, emphasizing the importance of these two variables. Meanwhile, in the full model of the decision tree, the history of previous medication also in line with the extension of the lesion as shown by the decision tree model below (the decision trees of other models including bivariate and short model shown in the published articles)

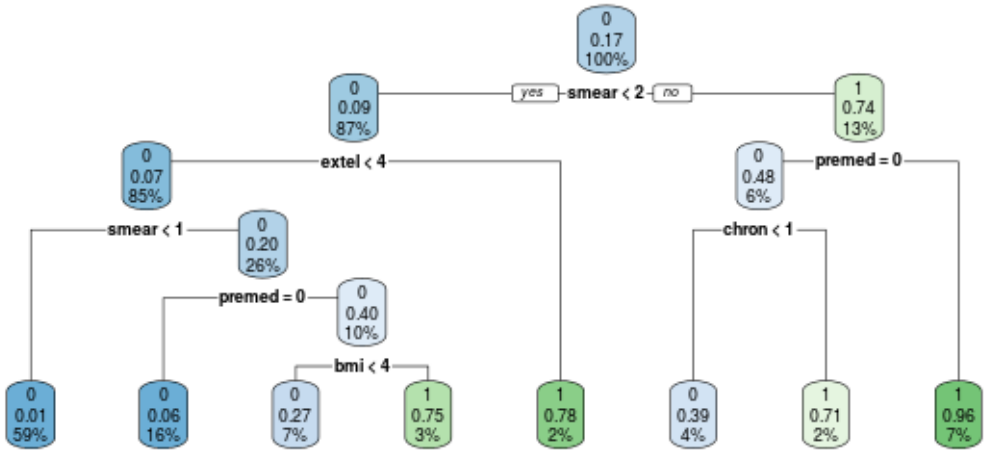


Figure 4.6 Decision Tree of Full model

The decision tree can illustrate the association of several variables. From the diagram above, the patient with a higher smear level followed an existing history of previous tuberculosis medication has a 96% possibility of having RR-TB. It also indicates a lower possibility of RR-TB for people with a non-extensive lesion on the radiology image. The table below shows the performance of another model with testing data.

Table 4.5. Performance of Other models with 15% training data (N=73)

Model	TN	TP	FP	FN	%Acc (95% CI)	% Sens (95% CI)	% Spec (95% CI)
LR full	53	16	1	3	95(87-98)	84 (60-97)	98(90-99)
LR Bivariate	52	16	2	3	93(85-98)	84 (60-97)	96 (87-99)
LR Short	54	14	0	5	93(85-98)	74(45-91)	100 (93-100)
DT Full	54	13	0	6	92(83-97)	68 (43-87)	100 (93-100)
DT Bivariate	54	13	0	6	92(83-97)	68 (43-87)	100 (93-100)
DT Short	54	10	0	9	88(78-94)	53(29-76)	100 (93-100)
RF Full	54	15	0	4	95(87-98)	79(54-94)	100 (93-100)
RF Bivariate	53	15	1	4	93(85-98)	79(54-94)	98(90-99)
RF Short	54	12	0	7	90(81-96)	63(38-84)	100 (93-100)
XGB Full	54	14	0	5	93(85-98)	74(49-91)	100 (93-100)
XGB Bivariate	54	15	0	4	95(87-98)	79(54-94)	100 (93-100)
XGB Short	54	14	0	5	93(85-98)	74(49-91)	100 (93-100)

Abbreviation: Acc = Accuracy; AUC = Area Under Curve; CI = Confidence Interval; DT = Decision Tree; FN = False Negative; FP = False Positive; LR = Logistic Regression; RF = Random Forest; TN = True Negative; TP = True Positive; XGB = Extreme Gradient Boost

The accuracy of all models ranging from 88-95% which lower than the best ANN model. The sensitivity is also inferior to the ANN model. However, the specificity is higher and reaches 100%. The full model and bivariate model of logistic regression showed the best performance as these models exceed 80% in all performance parameters with the Logistic Regression full model seen at the highest rank.

2. DEVELOPMENT OF THE WEB-BASED APPLICATION

A web-based platform was built with R code and using the shiny apps platform. The script is attached as an appendix. Component of the beta version web-based application including prediction page, HbA1c converter, BMI calculator, Brinkmann Index Calculator, and Explanation page. The application can be accessed at https://cuhasrobust.shinyapps.io/CUHASROBUST/ or using the QR code beside.

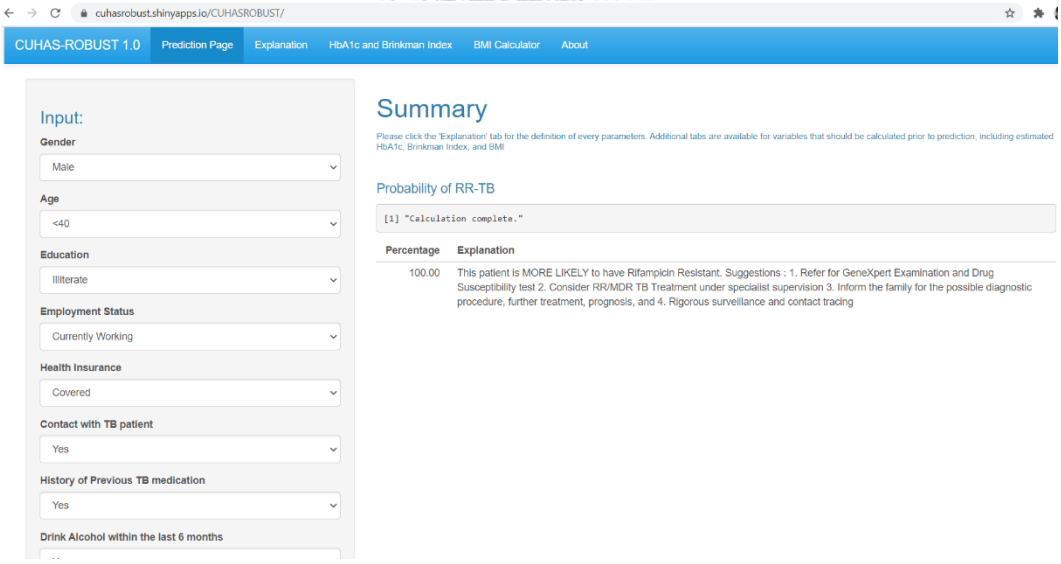


Figure 4.7 User interface of the application

The figure above is the first interface of the application where the user can input the parameter and start the prediction. The prediction with the interpretation will appear according to the results. The user can click the explanation table for further information.

The application could be accessed anywhere and anytime from the computer or the smartphone. By using the R script, the update of the model is feasible to improve the performance with the submitted data from the user. For the first version, this application used the standard server service by the Shiny server.

3. PROSPECTIVE DATA COLLECTION.

Suspected drug-resistant TB was referred to the study center with a total number of 402 participants. Eligibility criteria were applied. As 40 participants showed no growth on Lowenstein-Jensen culture, indicating a non-tuberculosis infection or problem with the sample management. Four people were admitted to inpatient care and scheduled for DST but died before the DST was conducted. As prior medication may alter the DST results, this study excluded 16 participants who received prompt treatment before DST. A total of 157 participants was successfully recruited for the prospective testing on the scheduled period as depicted by the flowchart below.

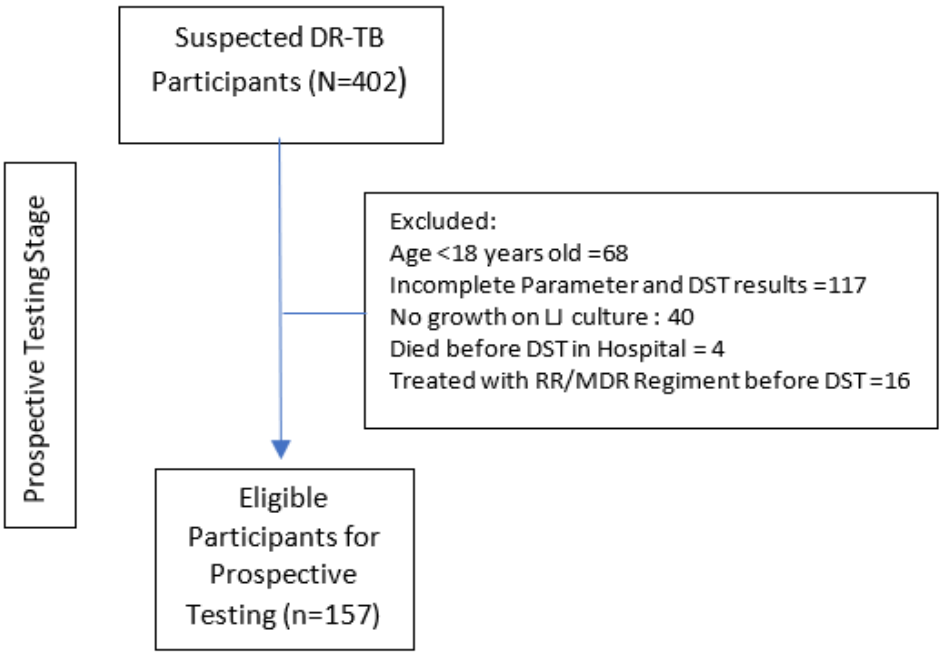


Figure 4.8 Flowchart of the prospective participants.

COVID 19 pandemic hinders the participant's recruitment and affected the type of patient being referred to the hospital. The only critically ill patient could be referred for examination and care. A baseline characteristic of the prospective participants confirmed a different pattern of variables, compared to the dataset for model building as shown in the table below.

Table 4.6. Participant's characteristic in prospective data (n=157)

Variable	Subset	RR + MDR (n=44)	Non-RR (n=113)	p value
Gender	Male	12	62	0.040
	Female	32	51	
Age (year)	<40	7	30	0.158
	40 and above	37	83	
	Mean ± SD	54.79 ± 13.51	51.60 ± 16.29	
Education	Illiterate	7	12	0.293
	Primary Education	12	20	
	Secondary Education	12	46	
	College degree and above	13	35	
Universal Health Coverage	Covered	33	86	0.884
	Uncovered	11	27	
Current Employment Status	Employed	26	66	0.938
	unemployed	18	47	
History of Drug Abuse	Never	41	112	0.067[&]
	Yes	3	1	
Contact with positive DR-TB case	Never	39	109	0.118[&]
	Yes	5	4	
HbA1c	<6.5	38	92	0.461
	>6.5	6	21	
History of Previous TB treatment	Never	20	81	0.002
	Yes	24	32	
HIV status	Reactive	2	2	0.313[&]
	Non-Reactive	42	111	
Brinkmann Index	Never Smoke	19	92	<0.001[&]
	1-600	23	20	
	>600	2	1	
Drink alcohol within one year	Never	41	113	0.021[&]
	yes	3	0	
Immunosuppressants use > 6 weeks	Never	38	105	0.218[&]
	Yes	6	8	
Number of Chronic Disease	0	25	64	1.000[&]
	1	19	47	
	2	0	2	
Body Mass Index (kg/m2)	<18.5	16	37	0.315[&]
	18-5-<23	24	67	
	23-25	1	7	
	>25	3	2	
Diagnosed as COPD	Yes	4	4	0.221[&]
	No	40	109	
Sputum Smear level	Negative or Scanty	14	45	
	1+	16	62	
	2+	7	5	<0.001[&]
	3+	7	1	
Presence of Cavitation	Yes	9	2	
	No	35	101	<0.001[&]
Extension of Lesion	0	11	81	<0.001[&]
	1	9	18	
	2	11	11	
	3	5	2	
	4	4	1	
	5	1	0	
	6	3	0	

Abbreviation: COPD (Chronic Obstructive Pulmonary Disease), DM (Diabetes Mellitus), DR TB (Drug-Resistant Tuberculosis). DST (Drug Susceptibility Test), HbA1c (Hemoglobin Glycated 1c) HIV (Human Immunodeficiency Virus), IQR (Interquartile Range), Max (Maximum), MDR (multidrug-resistant) Min (Minimum), SD (Standard Deviation). All tested with Chi-Square, except (& = Fisher Exact)

The prevalence of RR/MDR TB was higher compared to the prospective data, reaching 28% (44 per 157 participants). From the table above, several variables associated with the RR-TB were not shown in the prospective data. History of contact with the positive case, Hba1c, HIV status, chronic disease, BMI, and COPD was not associated with the drug resistance. On the other hand, a history of alcohol drinking showed a significant association.

A batch testing of all prospective data was conducted to evaluate the model on the new data. Several models were challenged, and the results were shown in the table below.

Table 4.7. Performance of all models in prospective data (n=157)

MODEL	TN	TP	FP	FN	%Accuracy (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)
ANN 2.2 Full	104	37	9	7	**90(84-94)**	84(70-93)	92(85-96)
ANN 2.1 Full	62	41	51	3	66(58-73)	93(81-98)	55(45-64)
ANN 2.1 Short	66	33	47	11	63(55-71)	75(60-87)	58(49-68)
ANN 2.2 Short	0	44	113	0	28(21-36)	**100(92-100)**	0(0-3)
Bivariate 2-2	58	37	55	7	61(52-68)	84(70-93)	51(42-61)
Bivariate 2-1	27	43	86	1	45(37-53)	98(88-99)	24(16-34)
LR full	112	17	1	27	82(75-88)	39(24-54)	**99(95-99)**
LR Bivariate	112	18	1	26	83(76-88)	41(26-57)	**99(95-99)**
LR Short	112	14	1	30	80(73-86)	32(19-48)	**99(95-99)**
DT Full	106	22	7	22	82(75-87)	50(35-65)	94(88-97)
DT Bivariate	106	22	7	22	82(75-87)	50(35-65)	94(88-97)
DT Short	110	16	3	28	80(73-86)	36(22-52)	97(92-99)
RF Full	107	13	6	31	76(69-83)	30(17-45)	95(89-98)
RF Bivariate	107	14	6	30	77(70-83)	32(19-48)	95(89-98)
RF Short	110	10	3	34	76(69-83)	23(11-38)	97(92-99)
XGB Full	108	8	5	36	74(66-81)	18(8-33)	96(90-99)
XGB Bivariate	107	9	6	35	74(66-81)	20(10-35)	95(89-98)
XGB Short	107	9	6	35	74(66-81)	20(10-35)	95(89-98)

Abbreviation: Acc = Accuracy; ANN = Artificial Neural Network; CI = Confidence Interval; DT = Decision Tree; FN = False Negative; FP = False Positive; LR = Logistic Regression; RF = Random Forest; TN = True Negative; TP = True Positive; XGB = Extreme Gradient Boost

From the table above, the Artificial Neural Network with full models shows higher accuracy among other models. The short ANN 2.2 model shows higher sensitivity, although it is not specific. The logistic regression models show better specificity with altered sensitivity (below 80%), thus, explaining why these models are inferior to the ANN model. Other models were not showing the best performance.

The bootstrap method was conducted to overcome the limited number of prospective data amid the COVID 19 pandemic. A total of 471 bootstrapped data was involved in further testing with the best model in each type of classifier, described in the table below.

Table 4.8. Performance of models in bootstrap data (n=471)

Model	True Negative	False Positive	False Negative	True Positive	%Accuracy (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)
DT Full	312	24	75	60	79(75-83)	44(36-53)	93(90-96)
RF Full	314	22	101	34	74(70-78)	25(18-33)	93(90-96)
LR Full	332	4	92	43	80(76-83)	32(24-40)	**99(97-99)**
XGB Bivariate	316	20	101	34	74(70-78)	25(18-33)	94(91-96)
ANN 2-2 Full	301	35	22	113	**88(85-91)**	**84(76-89)**	90(86-93)

Abbreviation: ANN (artificial Neural Network), DT (Decision Tree), GB (Gradient Boost), LR (Logistic Regression), RF (Random Forest), XGB (Extreme Gradient Boost)

From the table above, the artificial neural network 2-2 with full parameters outperforms other models with 88% accuracy, 84% sensitivity, and 90% specificity. The logistic regression model also exhibits a consistent finding with lower sensitivity and high specificity. The Random Forest model shows the lowest performance. In summary, the artificial neural network with full parameters, built with two hidden layers and two nodes in each layer shows the best performance and is selected as the core of the application.

4. USER EXPERIENCE ON THE WEB-BASED APPLICATION

A qualitative assessment with the in-depth interview as an additional stage of the study was performed to evaluate the utilization of the application. From the snowball invitation, 123 people responded, and 56 participants were interviewed. Repetition of the interview was done to one subject with a bad quality record. Retraction of the interview occurred in three subjects. The underlying reasons were an irrelevant response to the topic (two people), one participant wrongly used the application to predict pneumonia. As the tool should be used to predict the DST-confirmed participants, 20 participants were excluded. The final number of participants to be included in the analysis was 33. The summary of the interview was sent to receive any feedback, but no response was obtained. These participants provided 56 cases for performance analysis consists of 2 RR-TB and 6 MDR-TB cases. The description of the participant's characteristics is elaborated in the following table.

Table 4.9 Characteristic of application user and performance of the tool.

No	Variables	Statistic (n=33)		
1	Age	Mean (min-max) ± SD	33.12 (23-50) ± 7.57	
2	Years of working in primary care	Mean (min-max) ± SD	5.72 (1-19) ± 5.00	
		Group	Frequency	Percentage
3	Gender	Male	14	42.4
		Female	19	57.6
4	Occupation	Medical Doctor	12	36.4
		Head of Primary Care	4	12.1
		TB Manager	6	18.2
		Laboratory Technician	7	21.2
		Nurse	4	12.1
5	Education	Diploma	13	39.4
		Bachelor	17	51.5
		Postgraduate	3	9.1
6	Islands of Domicile	Bali + Nusa Tenggara	3	9.1
		Jawa	12	36.4
		Kalimantan	4	12.1
		Maluku and Papua	3	9.1
		Sulawesi	5	15.1
		Sumatera	6	18.2
7.	The total case for trial	Sensitive	48	85.7
		RR/TB	2	6.1
		MDR/TB	6	18.2
	Application Perception		Value	
1	Ease of Use	Mean (range) ± SD	8.18 (7-10) ± 0.57	
2	Clarity of Information	Mean (range) ± SD	8.27 (7-10) ± 0.56	
3	Feasibility to be implemented	Mean (range) ± SD	8.06 (7-9) ± 0.34	
4	Diagnostic Performance	Sensitivity MDR	66% (4/6)	
		Sensitivity MDR+RR	75% (6/8)	
		Specificity Drug Sensitive	83% (40/48)	
		Accuracy MDR+RR vs Drug Sensitive	82% (46/56)	

SD=Standard Deviation MDR=Multidrug-Resistant Tuberculosis RR=Rifampicin Resistant

This trial was performed in primary health care, where some of the participants have been working in the pertinent facilities for up to 19 years with an average working duration is 5.72 years. Most of the participants were female, dominated by medical doctors and bachelor graduates. The biggest portion of the participants lives in Jawa island. Three domains were assessed including the ease of use, clarity of information and the feasibility of application

to be implemented in their workplace. All domains showed an average score above eight where the highest score was in the clarity of information, particularly the definition of parameter and the interpretation of prediction, including the recommended approach for the case. The screening performance was also done with an accuracy of 82%, specificity of 83% but lower sensitivity of RR/MDR TB (75%) compared to the result in the model testing. The sensitivity was even lower when screening the MDR cases (66%).

5. QUALITATIVE FINDINGS

5.1 Tuberculosis care in the primary health center remains challenging.

The first section of the qualitative study is to explore the current situation of tuberculosis care in the primary health center, particularly addressing any intricate procedure. According to the dynamic model of transformed TB-to-MDR TB, a problem related to variable γ was explicitly conveyed from several statements below.

(ID, Medical Doctor 30 years old) “In our center, at least one new chronic TB case per month, and there is a need for further investigation to rule out any DR-TB possibility”.

(VN, TB Manager 45 years old) “The incidence of TB is at a steady number but recently, MDR-TB is now observed more. Now I am managing two new MDR-TB cases”.

The primary health care strain, coupled with the absence of facilities for proper treatment, may be one cause of the higher incidence of DR-TB. Because the service is provided free of charge to facilitate more patients receiving diagnosis and treatment for tuberculosis, hence the large influx of patients in rural areas can be observed. Meanwhile, private clinic charges a fee that adds to the overall expense of treatment costs, and it is a problem to those who have difficulty paying for their medical bills (181) This situation leads to an overcrowded healthcare system related to k or environmental capacity variable in the dynamic model).

(JY, Head of Primary Care, 40 years old) “We have more patients infected with tuberculosis than any other locations, and next to us is the private-run clinic. They also refer to us as some of their patients because these people are unable to afford care.”

As a result of the overcrowded healthcare facility, the workload increases and so the risk of infection, as shown by the following sentences:

(AH, Nurse, 36 years old) "We get more than 100 visits every day; right now, we have an outpatient TB clinic that is never empty." Even though I am not the TB manager, I feel obligated to assist S (the TB Manager) in dealing with her patients."

(IS, 24 years old, Nurse) "With so many patients in primary care and so few people wearing masks to avoid infection, we have no idea how dangerous the situation is, and this is a challenge not only to the health visitors but also to the workers who stay longer in primary care. Who knows if a healthy client would become infected with tuberculosis after coming here?"

Protecting and managing the patients, as well as educating them on infection control is difficult in the primary medical center. Furthermore, the primary care building is not as large as the hospital, complex adjustments to isolate the risky people are hard to be implemented.

(GG, Medical doctor, 30 years old)" As we look at the roots of DR-TB, we see that the majority of cases are the result of incomplete prior therapy. It is very difficult to persuade people to follow longer multiple regiments."

The new theme "policy" discussed the relationship between overcrowding in healthcare facilities, unfinished treatment (which was linked to variable c or effective cure rate in the dynamic model), and the frequency of DR-TB. According to a study conducted in primary care, inadequate surveillance systems are associated with altered tuberculosis management (182). And this is linked to the elevated burden and overcrowded healthcare facilities.

(WH is 46 years old and serves as a tuberculosis manager.) " As a nurse, I am responsible for overseeing the outpatient unit and struggle to find time to make home visits. It's very difficult to keep track of the treatment alone. There are some health volunteers, but the fact that they are doing it on a volunteer basis does not guarantee the consistency of their work." The insufficient diagnostic facility has been pointed out, and this is the issue symbolized by f (TB detection Rate) in the dynamic model. This condition is shown by an assertion.

(NS, 28 years old, doctor) " "I know sputum and radiology are valuable resources for diagnosing TB, but in primary care, we do not have the modality of radiology. When a patient is clinically suspected but does not have supporting sputum findings, we refer him or her to the hospital, but this again transfers the responsibility from primary care to the hospital, and not all patients can return for treatment."

Only 20% of patients encountered the expected diagnosis protocol during their initial visit to a health care provider, especially in primary care (183) and there is often some kind of conflict between primary care and hospital procedures. Although some primary care practices are attempting to expand their service modalities, the issue is not only one of tool availability, but also of supporting technician availability (184)

(AY, 50 years old, Head of Primary Care). ” Our primary care facility is fitted with an X-ray machine, but this equipment requires special care. Additionally, some staff members express worries about the radiation's safety. Due to the proximity of the referral hospital and the possibility that the operating costs will affect our overall budget, we choose to refer the patient instead.”

In summary, tuberculosis and drug-resistant tuberculosis continue to pose significant challenges in terms of diagnosis and treatment delivery, including therapy monitoring. Additionally, an inconsistent referral mechanism and insufficient health facilities lead indirectly to an increase in tuberculosis cases and health burden.

5.2 Diagnosis of DR-TB is time-consuming, costly, and inaccessible.

Drug-resistant TB diagnosis is a significant issue in primary care DR-TB management. The issue with DR-TB diagnosis was identified using a healthcare service delivery model. According to a report, the rate of sputum inspection in Turkey was approximately 71.6 % and the DST was approximately 25.8 % (185). These findings indicate more serious problems.

(FS, 23 years old, Laboratory Technician)” I admit that conducting the microscopic analysis is strenuous, as we must search for and count bacilli under continuous high-intensity light. Occasionally, I miscalculated the number of bacilli, which occurred during my quality control assessment.”

(JK, 36 years old laboratory technician)” I will consult with my physician to identify whether a patient has clinically suspected tuberculosis or not, to devote more attention to such cases. But that doesn't mean I ignore those unanticipated cases.”

The problem of sputum smear reliability in tuberculosis has been established. Numerous cases with negative or inconclusive findings but clinical suspicion were referred for radiology review, which lengthens the diagnostic process and degrades overall care quality. If there is a problem with the reliability of sputum analysis, those suspected of having DR-TB would be misdiagnosed.

(NS, 28 years old, Medical Doctor)." While DST is the gold standard for drug-resistant tuberculosis, GeneXpert makes it easier to confirm any cases with inconclusive sputum results, especially those with negative or sparse sputum results. However, given the scarcity of these instruments, I believe we can only depend on a reliable sputum smear test."

The DST is a labor-intensive and expensive reference standard. Although some centers provide the GeneXpert (a Nucleic Acid Amplification Test), the accessibility problem persists.

(SA, 29 years old TB Manager)." Waiting for the culture (DST) is a frustrating experience, as the center is too far away and takes a long time. However, they now have GeneXpert, which is even faster. Nonetheless, the patient should be referred to a doctor for further examination. All of which seems to be confusing in the context of the patient's experience."

(JK, 36 years old laboratory technician)" It is difficult to request GeneXpert now that it has been assigned to COVID 19 as well."

Uncertainty in diagnosis results in delayed care and inadequate medication, despite patient-centered causes, is still the primary underlying cause for delayed treatment (186). However, some physicians depend on pre-existing guidelines to address the problem.

(HJ, 32 years old, medical doctor)" I refer the patient to a pulmonologist for a more precise diagnosis and wait to see what happens. Typically, the desired treatment is defined on a referral form. Indeed, it continues to postpone treatment, however, adequate examinations are done in those instances."

(JB, 27-year-old medical doctor)" While I await a diagnosis, I will refer a suspected RR/MDR tuberculosis a prompt treatment."

Diagnostic difficulties are exacerbated by the reliability problem, an inadequate supply of rapid and DST tests, and lengthy waiting times, which result in delayed care.

5.3 Integrating the artificial intelligence to RR-TB Screening

Using the User Engagement Model (UEM), the CUHAST-ROBUST was introduced in the participant's workplace and assessed to see if it could alleviate the problems. The most significant aspect of the UEM's convincing architecture domain is the application's user interface.

(NN, 23 years old, Nurse) “It is extremely simple to use the program, whether on a cell phone or a computer.”

(HH, 34 years old, TB manager) “The various tabs with multiple functions are suitable, followed by a simple explanation.”

(MH, 24 years old, Medical Doctor) “By simply entering the details, I can quickly calculate the probability of RR-TB, given that the interpretation is provided.”

(NG, 23 years old, Laboratory Technician) “I don't need to install anything; I just need to click the connection and it'll open right up.”

The average score for "ease of use" is 8.18/10. However, some users' templates change, affecting the input process, suggesting a problem with the UEM's Personal Relevance factor.

(WH, 46 years old, TB Manager) “I open it on my phone and screen, but on my phone, I have to scroll further to press calculate.”

(ID, 30-year-old, Medical Doctor) “Some input function is given in slider and it is extremely difficult to do on a mobile phone”

In terms of information clarity, the majority of participants agree that the description and interpretation of the variable of the findings are straightforward, as indicated by an average score of 8.27/10.

(JY, 40 years old, Head of Primary Care) “At first, I assumed that I would have to measure the body mass index manually, but I later discovered that this program also includes a BMI calculator.”

The findings disclosed some new themes that shed light on the future effects of CUHAS-ROBUST as well as some concerns that must be addressed. These new themes are linked to the UEM's reputation and usability.

(YW, 36 years old, medical doctor) “I must admit, it is much more useful than using the criteria for suspecting DR-TB. It enhances my confidence in making decisions, referring cases, and initiating treatment.”

Artificial intelligence has been shown to improve clinical decision-making, resulting in appropriate and immediate clinical condition management(187). However, some issues must be addressed, such as detailed diagnostic performance assessment, interactive overview of how the program operates, and preference for the actual parameter over the estimated parameter.

(BC, 24 years old, Medical Doctor) “This application is fine, but since I don't know exactly how it works, I believe it requires further research in terms of precision, sensitivity, and specificity.”

(NA, 34 years old, Medical Doctor) “The application's embedded parameters are feasible. But, in terms of Hba1c, I believe it is preferable to obtain actual results rather than estimate them to obtain more reliable results.”

Another effect was seen in the data collection process and attempts to provide supportive circumstances. In UEM, these variables are related to the world and the personal domain.

(YM, 43 years old, Medical Doctor) “Perhaps the real difficulty is not the application. The accuracy with which we collect the information is based on the fact that the majority of the parameters are extracted from history taking. With minimal time to conduct a history and physical inspection, I believe we will miss important information.”

Due to time constraints, taking histories is limited. However, often gaining empathy is critical to obtain the patient's most profound and truthful response. This application affects compliance with medical protocols and discovering more innovative surveillance techniques.

(EG, Laboratory Technician (30 years old) “It compelled me to do one thing. I should concentrate on the sputum smear because it appears to be a significant indicator. If I am unable to provide the correct answer, the AI result is incorrect.

(JI, 30 years old, Head of Primary Care) “As the head of primary care, I believe I need to improve the availability of supportive modalities to ensure that my staff can provide the necessary details for the application. The application access is also completely free.”

(AM, 36 years old, TB Manager) “I believe I can use this for proactive monitoring and home visits, allowing more suspected patients to be screened without exposing other healthy people in primary care.

6. Cost-Effectiveness Analysis

6.1 Cost Calculation of the Drug-Susceptibility Test

As mentioned in the methodology, the calculation of the DST consists of cost per test, cost per positive results, and cost per negative results. The elements of the costs are as follows.

Table 4.10 types of equipment for the DST test

EQUIPMENT durable for 6000 test/year		
Digital Vortex	400	
Biosafety Level II Cabinet	3400	
Centrifuge	2000	
Thermolyne Culture Incubator	550	
Autoclave Gravity	3500	
Waterbath	1000	
Bunsen Burner Lamp	800	
Culture Bottle Washer	520	
Fogging Device	275	
Incinerator	4000	
Inspisator	5500	
Refrigerator	5500	
Microscope	500	
TOTAL	27945	**4.6575**

Table 4.10 elaborates on the equipment needed for conducting 6000 tests which can be done in a year. Most of the equipment has higher durability and when considering cost per test, investigation in equipment costs 4.6575 USD per test.

Table 4.11 Supplies for the DST test

Supplies 6000 examination/ year			
Alluminium foil heavy duty	21	Measuring cylinders	15
Adhesive tape roll	10	Microscope slides	102
Aspirator Flask	60	Nichrome Wire	50
Autoclave tape	112	Lab Coat	20
Beaker glass set 5 type	25	Disposable paper towel	30
Canister pipe cleaner	20	Pasteur pipet	15
Bowl	5	Pipette washer	90
Centrifuge tube	100	Blow-out pipet	18
Cotton wool	5	Reagent Bottle	150
Culture box	50	inspissation rack	100
Culture tube racks	45	Rubber teats	10
Laboratory pen	20	Scissors	10
Discard Bottle Splashproof	50	Self-filling syringes	400
Discard Dishes	20	Slide rack	20
Disinfectan	30	Slide storage	20
Filter Funnel Glass	32	Spatula Stainless Steel	30
Filter paper	36	Specimen Container	15
Forceps	10	Stain bottle	12
Glassware Elenmeyer	50	Staining Rack	10
Gloves	70	Stainless Steel Bucket with lic	40
Hand lens	7	Stirring rods	50
Inoculating loop	315	Testube glass	600
Paper for report	30	Lab Thermometer	40
Lens tissue	20	Lab timer	40
Masks	250	Volumetric flasks, glass	100
McCartney bottle	995	Wash bottle	50
Spill kit price	100	Other stationary	30
TOTAL	2488		2067
AVERAGE PER TEST			**0.75917**

Table 4.11 elaborates on the supplies needed for conducting 6000 tests which can be done in a year. The supplies are dominated by single-use devices and investigation in supplies costs 0.75917 USD per test.

Table 4.12 Protective Equipment for the DST test

Protective Equipment/100 Test	
Gloves 100	40
Mask for 100 examination	40
Disposable Gown 100	300
Headcap for 100 examination	30
Google	100
Boots	100
Disinfectan Agent	50
Spill kit price	40
TOTAL	**700**
AVERAGE	7

The protective equipment cost per test is high, reaching 7 USD per test. The protective equipment may vary across the laboratory level and the number of human resources involved.

Table 4.13 Treatment for specimen

Treatment for Specimen per 100 Test	
Glass and Plastic Wireset for 100 examination	500
Container per 100 examination	300
Chemical Preservation for 100 examination	5
Disinfectan phenol	10
Homogenization 100	15
Decontamination 100	15
Digestion with NALC 100	15
Culture unit per 100 examination	350
Culture DST unit Set	140
Reading and Differentiation with Niacin Test 100 test	100
Nitrate Reduction Test 100 test	100
Catalase Test 100 test	100
TOTAL	1650
AVERAGE	16.5

The treatment of specimen or sample needs specific process including homogenization, decontamination, digestion of sample particularly sputum and identification of mycobacterium from other bacteria, and drug sensitivity assessment which cost 16.5 USD per test.

Table 4. 14 Operational Cost per unit

Operational Per unit Test	
Quality Control	1
Utility	1
Person Cost Including :	2.8
Class II BSC testing	
Specimen Collection	
Culture Preparation	
Culture Observation	
Biochemical Test	
Reagent Management	
COST PER UNIT	4.8

Table 4.14 describes the operational cost including utility and payment for the staff. The average operational cost per unit/test is 4.8 USD. The total average cost of the drug susceptibility test is 33.71667 USD/ For further analysis of the cost-effectiveness, a different calculation of the positive case and negative case were also conducted.

In a real setting, the cost per positive and negative test is different because of the repeated procedure and contaminated specimen. A contaminated specimen particularly with bloodstain needs additional specimen collection and rigorous specimen treatment. Furthermore, positive cases need careful management, particularly in disposing of the culture. The cost of the negative case is lower as the drug-susceptibility test is frequently being skipped which accounted for one-third of the total cost as mostly no observed growth can be seen. From the total of 330 cases to be collected for analysis, the average cost of a positive case was 78 USD and the cost per negative case was 20 USD. These numbers are then put into the decision tree model.

6.2 Cost Calculation of the GeneXpert

The component of the GeneXpert cost calculation is comprised of actual costs and hidden costs. The hidden cost is related to the initial installment of the room and supporting device which sometimes is not incorporated into the final calculation of GeneXpert. The actual cost consists of operational, supplies, and the additional equipment needed.

The component of hidden costs including custom clearance, furniture, office modalities, software, air conditioning, electricity supports, container, plumbing, and miscellaneous fee. Since it is challenging to calculate the

hidden cost, the approximation of hidden cost is calculated from the study in Nigeria (188). By estimating the hidden cost can support up to 3000 examinations, the average hidden cost is at 3.24 USD/Test.

Table 4.15 Element of cost per GeneXpert Test

ELEMENT OF COST PER TEST	
Equipment	
Catridge	10
Mixture	0.5
Device (durable for 5000 test)	3
Supplies for Sample	1
Protective Equipment	3.5
Operational	3.4
TOTAL	21.4

As most of the GeneXpert tests are automatically done by machine, the cost of the GeneXpert is lower than DST. Adding the hidden costs, the average cost per test is 24.64 USD/Test. The cost of GeneXpert of positive cases and negative cases are different. The cost of positive cases is escalated because of the repeated test. Most of the positive cases may undergo repeated cases as the first case yielded negative results. By nature, the devices have three outcomes, negative, intermediate, and positive. All intermediate cases will undergo repeated tests for more than one time and on different occasions. By calculating the 330 cases, the average cost for the negative case (263) is 12.92 USD, whereas positive cases (67) reach 77.84 USD.

6.3 Cost of the Model.

The cost of the model is calculated depends on the structure of the parameter and the information needed. Cost of development is defined as the cost of collecting the data for model building, cost of developing the model, cost of building an application, and cost of web hosting paid annually. The table below elaborates on the cost of development.

Table 4.16 Cost to Develop the Model and Application

COST OF DEVELOPMENT	
Cost of Data Collection	
Registration	200
Training of Data Collector	200
Health Insurance of Data Collector	200
Protective Equipment	100
Data Access	1500
Data collector Service Fee	1000
Cost of Model Building	
Purchase of Software	500
Additional Course	50
Cost of Application Building	1000
Cost of Web Hosting/Year	1500
TOTAL	6250

The total initial cost is 6250 which could be assumed that this initial cost can accommodate up to 6250 tests. Hence the cost of development per examination is 2.08 USD dollar per test. This cost can be even lower across time.

Table 4.17 Cost of collecting parameter to be inputted in the model.

COST OF PARAMETER PER PATIENT	
General Physician Consultation	3
Sputum Smear	1
Radiology	5
Capillary Blood Glucose	1.5
HIV test	4
Peak Expiratory Spirometry	1
TOTAL	15.5

The cost of the parameter is based on the full model parameter. The capillary blood glucose is used for the approximation of HbA1c. Another cost to be incorporated is the cost of screening by a specific screener and supporting modalities including internet connection which capped at 3.5 USD per test. Hence the total average cost of running the application per patient is 21.08 USD. There is a difference between positive and negative cases as most positive cases underwent a parameter collection with advanced technology, thus increase the cost. The cost of negative cases (279) and positive cases (51) from 330 cases is estimated at 20 USD per negative case and 30 USD per positive case. Repeated examination, particularly the sputum smear, replacement of capillary blood glucose with HbA1C, ELISA test for HIV increases the cost in positive case.

6.4 Economic Assumption

These are the elements Included in the cost-effectiveness analysis. The prevalence of RR/MDR Tuberculosis to be used in this study is 20.6% (68/330) followed by the sensitivity and specificity of the model from the primary data. The global GeneXpert sensitivity and specificity were derived from a study in 2018. The approximation of quality-adjusted life years (QALYs) is based on untreated tuberculosis. The initial assumption is if the diagnosis is delayed, Hence tuberculosis treatment will also be postponed. There are three QALYs values to be incorporated into the model which are mortality, and morbidity (acute and chronic). Mortality defined as the QALYs lost when the disease is untreated and lead to the death of the patient. Meanwhile, the acute morbidity consists of QALYs lost due to the acute symptoms of tuberculosis if left untreated such as shortness of breath, fever, loss of body weight, etc. Chronic morbidity is related to the sequelae of tuberculosis such as post-tuberculosis obstructive syndrome.

Table 4.18 Economic Assumption in Model

Element	Value	Minimum	Maximum	Source
Prevalence RR/TB	20.6	10	23.4	Primary
Sensitivity CUHAS	84	76	89	Primary
Specificity CUHAS	90	86	93	Primary
Sensitivity Xpert	88	84	92	Dorman et al 2018
Specificity Xpert	97	94	99	
QALY to prevent mortality	0.22			
QALY to prevent Acute Morbidity	0.046			Miller et al 2009
QALY to prevent Chronic Morbidity	0.96			
Cost CUHAS (+)		All cost/ (+) cases		
Cost CUHAS (-)		All cost/ (-) cases		
Cost Xpert (+)		All cost/ (+) cases		
Cost Xpert (-)		All cost/ (-) cases		

The sensitivity and specificity of GeneXpert yielded from a study in 2018 (189)where the QALYs was derived on the study in 2009 assuming if the tuberculosis is left untreated(190)

6.5 Decision Tree Model

The decision tree model was built based on the different costs of various results (positive and negative tests), confirmed by the DST at the end of every scenario as depicted in the figure below.

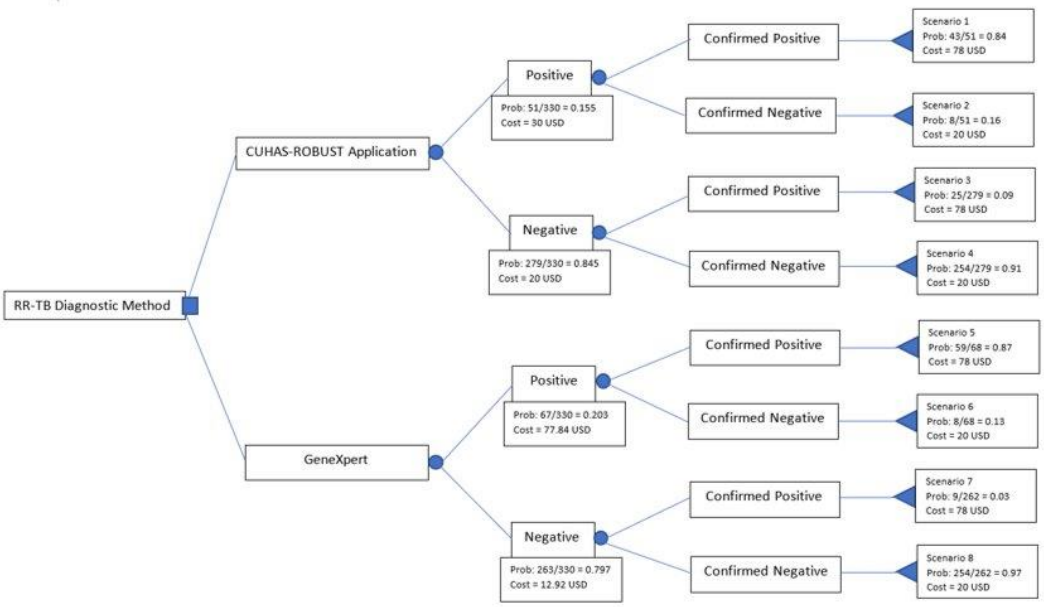


Figure 4.9 Decision Tree model of Cost-Effectiveness Analysis

Since the study implemented one patient with two different major scenarios, therefore, the prevalence of the disease remains similar for both scenarios. The different probabilities at the end of each scenario were calculated

from the sensitivity and specificity values of each modality. This decision tree yielded 8 different scenarios for the incremental cost-effectiveness ratio.

6.6 Incremental Cost-Effectiveness Ratio

Using the simulation by R program. There are three incremental cost-effectiveness ratio (ICER) values from the model. According to mortality, the cost of the model is 53.48575, whereas GeneXpert costs 57.72892. The Life Years of the Model are 0.0452925 and GeneXpert is 0.0441144. The incremental cost is -4.24317 followed by incremental life-years 0.011781. The ICER value is -3601.706137. This indicates that applying the model may save 3601.706137 USD per 1-unit QALYs gain for prevented mortality from detecting RR/TB earlier.

Furthermore, according to acute morbidity, the cost of the model is 53.48575, whereas GeneXpert costs 57.72892. The Life Years of the Model are 0.00947025 and GeneXpert is 0.00922392. The incremental cost is -4.24317 followed by incremental life-years 0.00024633. The ICER value is -17225.55. This indicates that applying the model may save 17225.55 USD per 1-unit QALYs gain for prevented acute morbidity from detecting RR/TB earlier.

And for chronic morbidity, the cost of the model is 53.48575, whereas GeneXpert costs 57.72892. Similar to the previous analysis. The Life Years of the Model are 0.19764 and GeneXpert is 0.1924992. The incremental cost is -4.24317 followed by incremental life-years 0.0051408. The ICER value is -825.391. This indicates that applying the model may save 825.391 USD per 1-unit QALYs gain for prevented chronic morbidity from detecting RR/TB earlier.

A sensitivity analysis was conducted to see whether different values of assumption yield different ICER results. Different prevalence and sensitivity values were applied. The scenario of different sensitivity values of the model and the final ICER calculation on QALYs gain in prevented acute morbidity, chronic morbidity, and mortality applied 100 USD/QALYs gain as willingness-to-pay value.

A sensitivity analysis of ICER of the model in terms of QALYs gained for prevented chronic morbidity was conducted. The sensitivity of the model below 80.6% shows a big ICER value that exceeds the willingness-to-pay. The ICER fell to the dominant intervention when the sensitivity starts from 80.6%.

In terms of QALYs gained for prevented mortality, the sensitivity of the model below 80.6% shows a big ICER value that exceeds the willingness-to-pay. The ICER fell to the dominant intervention when the sensitivity starts from 80.6%. This is similar to the analysis of chronic morbidity.

Last, the sensitivity of the ICER of the model in terms of QALYs gained from prevented acute morbidity was performed. The sensitivity of the model below 80.6% shows a big ICER value that exceeds the willingness-to-pay. The ICER fell to the dominant intervention when the sensitivity starts from 80.6%|

In all aspects (mortality, acute morbidity, and chronic morbidity), the sensitivity analysis demonstrates that a value of model with sensitivity from 80.6% is superior and less costly (fell in the right lower quadrant of cost-effectiveness analysis plane) compared to the GeneXpert and the model exceeds the willingness-to-pay value if the sensitivity of the model is lower than that.

Another scenario of sensitivity analysis was conducted according to different prevalence according to the model. The sensitivity analysis concerning different prevalence was conducted according to the QALYs gained for prevented mortality. The model fell to the dominant segment when the prevalence of the disease is around 14.8%-23.3%. The ICER exceeds the willingness-to-pay value when the prevalence of RR-TB per suspected DR-TB above 27.2%. There is a similar finding in terms of ICER of QALYs gained in prevented acute morbidity while adjusting the prevalence. The acceptable prevalence is 14.8%-23.3% to demonstrate the model as a dominant intervention. However, prevalence above 24% surpasses the willingness to pay limit, which somehow lower than ICER of mortality. According to chronic morbidity, the prevalence of 14.8% to 23.3% shows superiority and lower cost compared to GeneXpert. However, even if the prevalence of the disease is up to 100%, the ICER does not exceed the willingness-to-pay, where the ICER of the 100% prevalence is 66.68 USD / QALYs gain from prevented chronic morbidity.

The last scenario was applied using the average cost of GeneXpert, Model, and DST. It yielded ICER -3021.815 USD per QALYs gained from prevented mortality, -14452.16 USD per QALYs gained from acute morbidity and -692.499 USD per QALYs gained from chronic morbidity. All of which consistent with the calculated scenario concerning the different costs per result.

CHAPTER 5

DISCUSSION AND CONCLUSION

1. ARTIFICIAL INTELLIGENCE MODEL IS A PROMISING TOOL FOR DRUG-RESISTANT TUBERCULOSIS SCREENING.

This study addressed the parameter of the AI model for RR TB, including demographic, clinical, and radiology information as categorical input. The plausible reason why this study did not involve radiology images as the source of the parameter is due to the intricate process. One of the essentials points is the complicated pre-processing procedure which focuses on capturing a good quality image (by adjusting the voltage, the current x-ray tube, and imaging exposure time)(191), and recognition of structure using image descriptors (192) which may promote a better result.

Radiology imaging is not common due to radiation exposure (193) and only done to confirm unexplainable respiratory symptoms(194), making the scarcity of data for model building. These circumstances also worsen by interrater reliability issues from the radiologist (195).

As pre-processing steps and complex model structures are the key challenges of the radiology model, the clinical data model obstacles begin from the data collection. The accuracy, completeness, and comparability of the patient-based data in the medical record still become a focus of several studies (196). The data from medical records, especially the history-taking information on the initial assessment of the patients, can be affected by recall bias or refuse-to-answer behavior. For example the history of imprisonment where people may feel reluctant to disclose this information. Some demographic data could be obtained from an electronic database by providing the identity number but once again, the use of personal information for the non-medical purpose might be limited and consent should be gained for the intended purpose, except the hospital explains that the medical record information can be disclosed for research purpose. Besides the recall bias, the things that hinder the completeness of the information are the limited time of history taking and physical examination. A study in Turkey discloses the need to provide a longer time for patient assessment and the shortened time was mainly due to overcrowding. History of disease in the patient even recorded for less than 40% in this study (197)

Another aspect that attenuates the quality of data is interrater reliability. Different physicians may interpret the signs and symptoms according to their experience. The insufficient and lack of reliability may lead to an unsatisfactory prediction when building a predictive model using patient-based data. Some predictors that prone to this issue are abnormal physical examination. A pulmonologist can distinguish fine crackle sound compare to a fresh-graduate physician. Furthermore, a retrospective study over four decades in Wellington shows that physical examination observation declined by 34% as well as the number of body systems examined (198) indicates more significant information could be missed from general examination compare to the physical examination in the past time, leaving a decreased meaningful significant findings for supporting information.

The strong aspects of this study were the data collection method and the reference test. The rigorous methods of screening the eligible participants through electronic medical records were performed with ICD code and elaborate standard procedures and quality control applied. The electronic medical record system provides a fast screening process, and preserved data quality(199). The exclusion was made to the one who received the prompt treatment before DST. Despite different DST procedures were introduced at a certain time, only the participants who underwent the DST with the LJ method were selected. reducing the heterogeneity of DST results due to different processes. In this study, all the negative results showed a sensitive result to all regimens.

Selecting the best predictors and determine the source is also critical. Despite a global review that has successfully addressed the associated factors, not all factors were presented in a certain population. For example, alcoholism may not be popular in certain countries and areas with high religious engagement. Model build from hospital dataset has less generalizability when implemented in a primary care setting as most of the patients admitted to the hospital were at a later stage, hence, clinical manifestations are more prominent than the patients in primary care, leaving the possibility of underdiagnosis when the model implied to this setting.

This study deciphers the robust way to select the best predictor, including the bivariate assessment, and based on the plausible relationships of the predictor to the outcome. The issue of generalizability occurs in this study as not all the parameters are locally relevant, and the prospective testing was conducted in the same center. This is why in the future; the trial should be expanded across the country.

One essential aspect is drug-resistant testing. Sample collection is an important thing especially the sputum quality. There are various methods for culture including agar and liquid culture. The interpretation method also differs, either using the proportion method, absolute or minimum inhibitory concentration. The proportion method is still the most preferred method for DST. Various method affects the reproducibility of the *mycobacterium*, thus, explain why the sensitivity of DST in detecting DR-TB is near-perfect (98.5%, 96.8%, 93.9% and 94.0% for Isoniazid, Rifampicin, Streptomycin, and Ethambutol respectively). The minimum inhibitory concentration method should be adjusted according to the strain of TB as some of the specific strains of TB will be undetected and this is the weakness of this method(200). This study relied on the solid culture and excluded those with negative cultures who received prior treatment which reduces the underdiagnosis. Initial treatment with recommended drug-resistant regimens sometimes preceded the DST as it is time-consuming and earlier treatment shows a better prognosis. There is a few difference between chronic tuberculosis and drug-resistant tuberculosis regiment, explaining the reason why giving initial treatment is common in suspected DR-TB.

Most of the clinical data were presented in continuous data such as age, or body mass index. Discretization into certain categories enhanced the learning process of the model and less computing cost but discretization should be followed by reasonable judgment. Classification of age should be done according to the prevalence of DR-TB. A global systematic review reported that a cutoff of 40 years old is significantly important(11). Some risk factors could be elaborated such as determine the smoking behavior which could be explained using Brinkmann Index and grading the smoker to certain categories. This discretization facilitates more meaningful information to be considered.

The imbalance of positive and negative cases in the dataset may affect the performance of the model, particularly in very rare diseases with limited positive cases (127). In this case, this situation occurred where the proportion of disease in the dataset is almost twice the actual proportion. Using the true proportion (10.26%) may introduce a bigger imbalance problem, while the ideal way is to create a balanced proportion of positive and negative cases (50:50). Using the bigger prevalence in the dataset (18.27%) is better despite not representing the total data proportion. The most essential thing is to have a bigger variability of data, but the variability is not always linear with the number of samples.

To achieve a bigger number, therefore, the missing data should be handled as machine learning will not process the missing data. The imputation method of missing data introduces risks, particularly when the proportion of the sample with missing data is too high. A SMOTE technique is used to overcome imbalance, by either adding the number of minority cases (in this situation, the positive case) or remove the majority case from the total population(172)

There was one issue in SMOTE implementation. The possible SMOTE technique is to listwise the negative test in the dataset with SMOTE approach rather than synthesize positive cases, resulting in a lower number of participants in the dataset. This is why SMOTE is not feasible

Limited dataset still hinders model development, especially for validation purposes. The issue of different validation methods should be considered as some variation of validation methods can introduce bias, such as using the k-fold cross-validation versus nested cross-validation and train/test splitting (201). This study applied the bootstrap method to yield the bigger number of the sample which has the same confidence interval as the initial sample. Although to expand the generalizability of the model, there is a need to challenge the model with various data across the country.

This study applied a similar protocol of model building to all different classifiers, including the data splitting and validation technique. Overall, the ANN model is preferable over other models, concerning the clinical data as a parameter. Therefore, for future model building, Artificial Neural Network is the preferred model.

The disadvantage of ANN is the ANN unable to sort the important feature/parameter of the model, as shown by other models such as XGB or even classification tree. However, building ANN with the new and latest library will also allow the assessment of important features such as the SHAP library.

Deployment service of this model into a simple web-based or mobile-based application is expected, which can be implemented for screening purposes at healthcare service and assessing the generalizability of the model in various settings. This study has successfully deployed the model into an application (CUHAS-ROBUST) which can be accessed from a computer and mobile phone. Supported by wide internet dissemination, AI-based screening is now feasible to be implemented, even at the most remote healthcare provider.

It is really important to test whether this ANN Model could also screen the other types of DR-TB and to assess the performance in expanded testing, including detection of MDR-TB or even XDR and TDR TB. Hence this tool will have a higher impact in detecting more variants of DR-TB.

In a summary, the machine learning and deep learning model particularly the Artificial Neural Network model possess a good screening ability, particularly when built with a higher number of well-processed and reliable data. This study emphasized the possible role of clinical and demographic data as good predictors of rifampicin-resistant tuberculosis which could be implemented in any level of healthcare service.

2. THE AI-BASED SCREENING IS A FEASIBLE AND ACCEPTABLE PROCEDURE.

Based on the qualitative finding, AI-based screening can be implemented in healthcare services but not without several issues. This study identified the problem of DR-TB including the rising of the case, the inadequacy of the health system to provide health service which leads to loose monitoring of therapy, and possible staggering disease transmission. Similar findings were found in Vietnam where a lack of TB screening capacity was observed in district hospitals and the conflicting policies appears often due to miscommunication between the policymakers and the executive officers. The discrepancy of private and public healthcare is seen, specifically in MDR-TB reporting where the private sectors tend to not comply with the surveillance protocol. In detailed key findings, Vietnam faces failure to identify presumptive MDR cases (202). The current guideline in Indonesia for presumptive DR-TB is based on a list of the condition including positive contact with DR TB, HIV- reactive, chronic TB and it is a very broad criterion to narrow down the eligible people for further testing which available at a limited number.

This study successfully emphasized the main problem of DR-TB (with the health service delivery model) which is the diagnosis problem. In this study, according to the user engagement model, the CUHAS-ROBUST has a good engagement and can tackle some of the RR-TB screening problems. It also achieved its purpose by providing a fast clinical-decision-making function (187) which overcomes the prolonged diagnosis time and demonstrates more than 80% accuracy to predict MDR+RR TB based on the data given by the participants. Besides, the indirect impact also addressed from this study including enhancement of clinical procedure compliance including proper history taking and laboratory examination, as well as enhancing plans for healthcare tools provision. Embedding CUHAS-

ROBUST into active surveillance is the new concept expressed by the participant, expanding the possibility of AI integration to further aspects of healthcare.

A strong point of this study is a rigorous qualitative method where the researcher accommodated various professions from different provinces, hence, increasing the generalizability of the finding (in terms of acceptance by the user). The limitation of this study was the participants were unaware of the preliminary performance of CUHAS-ROBUST. Participant's expectations of certain diagnostic performance may affect the user experience. Moreover, the researcher did not measure the digital literacy of the participants which might affect the user experience.

In conclusion, CUHAS-ROBUST, an artificial intelligence-based screening tool, introduces benefits for RR-TB screening, and it is relevant to what the private sectors are expected to(203). The researcher projected that implementing this screening tool also affects other aspects of the healthcare system, including the quality of care improvement and enhancing other TB-related policies.

3 THE AI-BASED SCREENING IS COST-EFFECTIVE.

Based on the cost-effectiveness analysis, although the justification using the limited data was insufficient, still provides clear evidence that AI-based screening can be implemented in a place where the existing rapid test such as GeneXpert is unable to perform.

The calculation of DST is based on the proportion method which is not the newest technique. The microscopic observed drug-susceptibility and MGIT are now introduced in clinical practice due to faster results with the trade-off of accuracy. The latest tests may provide lower costs, but in this study, the standardized proportion method was preferred.

The cost of GeneXpert was calculated based on the recommended procedure per test, adjusted by Indonesia's price. Most of the positive cases that needed repeated tests were the test with intermediate results or patients with negative smears. Unfortunately, no further analysis of incremental cost for the second test was conducted in this study. The cost of GeneXpert is lower compared to the value in a systematic review (24.64 USD versus 29.8 USD per test)(204). There is a policy to reduce the cartridge price for countries with high drug-resistant burdens. Moreover, this study also included a potential hidden cost which is uncommon to be calculated.

The cost of the model might vary across time. The fixed value of investment cost will introduce a decremental development cost per test. Different costs of clinical examination may also affect the total average cost. If a person wants to get the approximate HbA1c value using the capillary blood glucose, the cost will be even lower and vice versa. Furthermore, a repetitive procedure such as a sputum smear might increase the cost of the model. The cost of sputum smear is slightly higher compared to the estimated price from a study assessing tuberculosis in 36 countries which are 0.61 per test. But this price was set in 2012. Adjusting the inflation rate and the current USD value (2020), the cost of sputum smear will be 0.57 per test(205). By setting the cost of sputum smear to 1 USD per test according to the standard fee, it will accommodate the repetitive sputum test, and escalated estimated cost of the model is avoidable. Factors that contributed to the lower estimated cost of the model are the rapid test provided in primary care. Using ELISA for HIV assessment and electronic spirometry for lung function assessment will increase the cost and all these modalities are not provided in primary care.

The cost-effectiveness analysis in this study has several issues. This study created a scenario if the patient undergoes two different scenarios whereas the best way is to assign the individual with different treatment. Furthermore, the assumption of the cost-effectiveness analysis might not be appropriate including using the QALYs of untreated tuberculosis as the approximation of QALYs of delayed drug-resistant tuberculosis diagnosis. This cost-effectiveness analysis is also based on the view of the health provider, so only the direct cost of the examination can be calculated while the indirect cost may have a significant proportion that cannot be ignored. Devaluation value and discounting techniques were also not implemented in this study.

It is also important to test the overall performance of the model and considering the prevalence of the RR-TB per suspected case. This new modality might not be beneficial in the area where the prevalence is lower or too high which the ICER surpasses the willingness-to-pay limit. And there is a need to improve the sensitivity of the tool as the lower sensitivity tool is no longer cost-effective. In this study, the model is dominant if implemented in the area where the prevalence of RR-TB per suspected cases ranging between 14-23%. It is also important to maintain and update the sensitivity of the tool above 80.6%

4. CONCLUSION AND RECOMMENDATION

Based on the explanation, here are the conclusion and the future recommendation based on the study result.

a. It is essential to preserve the quality of clinical data by maintaining a good clinical examination and standardized medical procedures.

b. It is pivotal to disseminate the supportive modalities to increase the health service quality and to obtain more reliable parameters.

c. Preservation of clinical data through the digital form is important to support the big data analysis and model building in the future, particularly in establishing a clinical-decision-making.

d. Artificial Intelligence model is a promising tool to be implemented in healthcare service, particularly as a screening tool.

e. Reception of AI-based intervention is high, and the healthcare staffs are willing to adopt the new technology.

f. The AI-based is proven to be cost-effective if there is room for performance improvement and concerning the prevalence of the disease.

APPENDIX

1. Book Code of Variables

No	Variables	Value	Code
1	Age	Continous	Continous
2	Age group	Binary, Discretization of Age	Example : <40 (0) above >40 (1)
3	Gender	Binary	Male (1), Female (0)
4	Education	Ordinal	0 (illiterate) 1 (primary education) 2 (secondary educatio) 3 (diploma/bachelor postgraduate)
6	Health Insurance	Binary	0 (No) 1(Yes)
7	Marital Status	Binary	0 (Married) 1 (Single)
8	Employment	Binary	0 (employed) 1 (unemployed)
9	Income Level	Continous	Continous
10	Diabetes Duration Years	Continous	0 for no Diabetes
11	Have Diabetes	Binary	0 (No) 1(yes)
12	HbA1C	Binary	0 (Below 6,5%) 1 (Above 6,5%)
13	COPD	Binary	0 (No) 1(yes)
14	Body Mass Index	Ordinal	5 (Underweight) 4 (normal weight) 3 (overweight) 2 (class I obesity) 1 (class II obesity)
15	HIV Status	Binary	0 (No) 1(yes)
16	Smoking	Ordinal	0 (Brinkman 0) 1(Brinkman 1-600)

			2(Brinkman>600)
17	Alcohol Consumption	Binary	0 (No) 1(yes)
18	Immunosuppressive use	Binary	0 (No) 1(yes)
19	History Of Drug Abuse	Binary	0 (No) 1(yes)
20	Adverse Drug Reaction	Binary	0 (No) 1(yes)
21	Adherence Therapy	Binary	0 (No/ Never treated) 1(yes)
22	Presence of Chronic Disease	Binary	0 (No) 1(yes)
23	Sputum Smear Level	Ordinal	0 (Negative) 1 (Scanty) 2 (1+) 3 (2+) 4 (3+)
24	Zone Involvement	Continous	1-6
25	Presence of Cavity	Binary	0 (No) 1(yes)
26	Number of Cavities	Continous	Continous
27	History of Contact	Binary	0 (No) 1(yes)
28	Household Crowd	Continous	Continous
29	DDD	continous	continous

2. General Code For Cost-Effectiveness Analysis in R (Example for QALYs gained from prevented mortality with Sensitivity Analysis)

```
##################################

#### Vector of parameter inputs

##################################

input <- data.frame(

  p.DA = 0.1545,      # Probability of tested positive DST with Model
```

```
  p.DB = 0.203,        # Probability of tested positive DST with GeneXpert
  p.TPA = 0.84,        # Probability of confirmed positive with Model
  p.TPB = 0.87,        # Probability of confirmed positive with GeneXpert
  p.TNA = 0.91,        # Probability of confirmed Negative with Model
  p.TNB = 0.97,        # Probability of confirmed Negative with GeneXpert
  ly.Cured  = 0.44,      # Life years after being cured (based on assumption table)
  ly.NotCured  = 0.22,  # Life years after not being cured ( on assumption table)
  c.MP = 30,           # Costs of having positive test Model
  c.MN = 20,           # Costs of having Negative test Model
  c.GP =77.84,         # Costs of having positive test Genexpert
  c.GN =12.92,           # Costs of having Negative test Genexpert
  c.confneg = 20,     # Costs of being confirmed negative
  c.confpos = 78,    # Costs of being confirmed positive
  wtp    = 100           # Willingess to pay per life year gained
  )


#####################################################
#### Wrap decision tree into a function ####
#####################################################
dec_tree <- function(params){
  with(
    as.list(params),
    {

      # Expected probabilities for each pathway
      ### Pathways for Treatment A
      ep4 <- (1 - p.DA) * p.TNA              # Expected probability for Pathway 3
```

```
ep3 <- (1 - p.DA) * (1 - p.TNA)        # Expected probability for Pathway 4

ep1 <- p.DA * p.TPA                    # Expected probability for Pathway 1

ep2 <- p.DA * (1 - p.TPA)              # Expected probability for Pathway 2


### Pathways for Treatment B

ep8 <- (1 - p.DB) * p.TNB              # Expected probability for Pathway 8

ep7 <- (1 - p.DB) * (1 - p.TNB)        # Expected probability for Pathway 7

ep5 <- p.DB * p.TPB                    # Expected probability for Pathway 5

ep6 <- p.DB * (1 - p.TPB)              # Expected probability for Pathway 6


# Total costs for each pathway (unweighted)

### Total costs for Treatment A

tc1 <- c.MP + c.confpos                # Total costs for Pathway 1

tc2 <- c.MP + c.confneg                # Total costs for Pathway 2

tc3 <- c.MN + c.confpos                # Total costs for Pathway 3

tc4 <- c.MN + c.confneg                # Total costs for Pathway 4
```



```
### Total costs for Treatment B (unweighted)

tc5 <- c.GP + c.confpos                # Total costs for Pathway 5

tc6 <- c.GP + c.confneg                # Total costs for Pathway 6

tc7 <- c.GN + c.confpos                # Total costs for Pathway 7

tc8 <- c.GN + c.confneg                # Total costs for Pathway 8


# Expected Total Costs for each Treatment strategy is the sum of the weighted values

# (probabilities of each pathway multiplied by the total costs of each pathway)

### Expected Total Costs for Treatment A

etc.Model <- (ep1 * tc1) + (ep2 * tc2) + (ep3 * tc3) + (ep4 * tc4)
```

```
### Expected Total Costs for Treatment B

etc.GeneXpert <- (ep5 * tc5) + (ep6 * tc6) + (ep7 * tc7) + (ep8 * tc8)


# Expected Life Years for each Treatment strategy is the sum of the weighted values

# (probabilities of each pathway multiplied by the Life Years of each pathway)

### Expected Life Years for Treatment A

ely.Model <- (ep1 * ly.Cured) + (ep2 * ly.NotCured) + (ep3 * ly.Cured) + (ep4 * ly.NotCured)


### Expected Life Years for Treatment B

ely.GeneXpert <- (ep5 * ly.Cured) + (ep6 * ly.NotCured) + (ep7 * ly.Cured) + (ep8 * ly.NotCured)



# Expected total costs, expected life years, incremental costs, incremental life years, and ICER lists

C    <- c(etc.Model, etc.GeneXpert)

LY   <- c(ely.Model, ely.GeneXpert)

IC   <- etc.Model - etc.GeneXpert

IE   <- ely.Model - ely.GeneXpert

ICER <- (etc.Model - etc.GeneXpert)/ (ely.Model - ely.GeneXpert)


names(C)    <- paste("C", c("Model", "GeneXpert"), sep = "_")

names(LY)   <- paste("LY", c("Model", "GeneXpert"), sep = "_")

names(IC)   <- paste("Incr Costs")

names(IE)   <- paste("Incr Life Years")

names(ICER) <- paste("ICER")


# Generate the ouput
```

```
    return(c(C, LY, IC, IE, ICER))
  }
)
}

#### Now, we can use the function "dec_tree" with the inputs to estimate the ICER and its corresponding values
dec_tree(input)

#####################################################
#### One-way Sensitivity Analysis for Various Prevalence and Sensitivity
#####################################################
# In the base-case, the Probability of Positive of Model is 0.84. The range is 0.76 to 0.89.
p.TPA_r  <- seq(0.76, 0.89, length.out=14)    # Perform 11 calculations between 0.00 and 0.100. This is for sensitivity
            analysis for different sensitivity
p.TPA_r
p.TPB_r  <- seq(0.84, 0.92, length.out=9)    # Perform 11 calculations between 0.00 and 0.100.
p.TPB_r
p.TNA_r  <- seq(0.86, 0.93, length.out=8)    # Perform 11 calculations between 0.00 and 0.100.
p.TNA_r
p.TNB_r  <- seq(0.94, 0.99, length.out=6)    # Perform 11 calculations between 0.00 and 0.100.
p.TNB_r
p.DA_r  <- seq(0.1, 1, length.out=100)    # Perform 100 calculations between 0.00 and 0.100. This is for the sensitivity
           analysis for different prevalence
p.DA_r

## Generate matrix of inputs for decision tree (Replace variable 3 which is TPA with the ranges)
m.owsa.input <- cbind(p.DA = p.DA_r, input[-3])
```

```
m.owsa.input


## Run model with captured Total Costs across the ranges 0.00 to 1.00 for probability positive with model

outcomes_TC <- t(apply(m.owsa.input, 1, dec_tree))[ , 1:2]  # t(x) is the transpose function [column 1 = C_TxA in the
            output]

outcomes_TC


#### ========== NOTE: Understanding the apply function ========== ####

apply.table1  <- (apply(m.owsa.input, 1, dec_tree)) # Note: This will give us 7 rows and 11 columns.

apply.table1


apply.table2  <- (apply(m.owsa.input, 1, dec_tree))[ , 1] # Note: You get different columns than the transpose matrix;
            we don't want apply.table. We want outcomes_TC. The [ , 1] denotes the 1 column from apply.table1.

apply.table2
```

3. Code, Dataset, and Developed model can be accessed in publication (176)

4. Criteria for Diagnosing Diabetes

Fasting Plasma Glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake during a period of 8 hours.*
OR
2-hours PG ≥200 mg/dL (11.1 mmol/L) during oral glucose Tolerance Test. The test should be conducted according to WHO recommendation, by giving a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
Haemoglobin A1C ≥6.5% (48 mmol/mol). An NGSP-certified laboratory and standardized to the DCCT assay is expected to perform this test.*
OR
Thorough history-taking, the presence of classic symptoms of hyperglycemia or any event of a hyperglycemic crisis, random plasma glucose showing ≥200 mg/dL (11.1 mmol/L).

*Two abnormal results should be obtained either from the same sample or two different samples when the unequivocal hyperglycemia is absent

5. Criteria for Diagnosing COPD

GOLD	Condition: testing after bronchodilation and FEV1/FVC < 0.7		
	1	Mild	FEV1 ≥ 80% predicted
	2	Moderate	50% ≤ FEV1 <80% predicted
	3	Severe	30% ≤ FEV1 <50% predicted
	4	very severe	FEV1 <30% predicted (until 2011. also fev1 <50% and chronic hypoxemia with pao2 < 60 mm hg)
ATS/ ERS	Condition: Tiffeneau Index below 5th percentile for normalized distribution (LLN)		
	1	Mild	FEV1 ≥ 70% predicted
	2	Moderate	FEV1 60–69% predicted
	3	moderate to severe	FEV1 50–59% predicted
	4	Severe	FEV1 35–49% predicted
	5	very severe	FEV1 < 35% predicted

GOLD. Global Initiative for Chronic Obstructive Lung Disease; ATS. American Thoracic Society; _ERS. European Respiratory Society; FEV1. forced expiratory volume in one second; _FVC. forced vital capacity; LLN. the lower limit of normal (206).

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