ABSTRACT

Tuberculosis (TB) is an infectious disease mainly caused by Mycobacteria tuberculosis. It affects the respiratory system and may spread to the other organ. Due to the nature of the bacteria, infection of this species may cause a long-term TB, causing it a challenge for a full clearance. The disease has existed throughout the history, and BCG vaccine has been developed to control the spreading. Most developed countries have successfully eradicated TB. However, Indonesia is currently ranked second place for this disease, making it as a pressing matter to eradicate. This study is conducted to investigate and gather deep insights about the problems in eradicating TB in Indonesia. Identify part of the biodesign method is employed in the study to elucidate the complexity of healthcare issue of TB in Indonesia. The study discovered that there are three pillars’ sectors need to be addressed: education, healthcare facilities and services, and government. For successful eradication, synergistic approach to all pillars at the same time are essential. The needs statements formulated in this study could be the stem of innovation in TB.

Keywords: Biodesign; eradication; healthcare; tuberculosis; vaccine

INTRODUCTION

Tuberculosis (TB) is one of airborne infectious disease that mainly infects the respiratory system. Infection may cause symptoms such as prolonged cough (≥2 weeks) hemoptysis, low-grade fever, night sweats, loss of appetite, malaise, fatigue and weight loss (Acharya et al., 2020).

It is commonly caused by Mycobacterium tuberculosis (MTB). This bacterium is easily spread through coughs, sneeze, and saliva droplets from the infected person (BañUls, Sanou, Van Anh, & Godreuil, 2015).

In the infection process, the pathogen-associated molecular patterns (PAMPS) of MTB binds to the pattern recognition receptors (PPRs) on the alveolar macrophage cells. As a result, the bacteria are internalized and resides within the phagosomal membrane (Heemskerk, Caws, Marais, & Farrar, 2015). Naturally, as infection happens, inflammatory respond occurs to control the growth and eliminate the bacteria. In the attempt to evade the host defense, the bacteria utilize the ESAT-6 secretion system-1 (ESX-1) to disrupt the phagosomal membrane, preventing phagolysosome process and
release its products into the macrophage cytosol.

MTB maintain its proliferation activity while residing in the macrophage, diseminate and infect surrounding cells upon necrosis, including the interstitial tissue of the lungs through direct infection to the alveolar epithelium or the migration of the infected macrophages to the lung parenchyma (Pai et al., 2016). The presence of immune cells including T cells attempts to halt MTB proliferation and form granuloma to contain the bacteria, eventually become stable or latent. In circumstances where the host defense fails to clear the infection, latent bacteria may be reactivated, damaging nearby bronchi and may disseminate to other organ (Acharya et al., 2020; Zuiga et al., 2012).

TB is believed to have emerged 70,000 years ago and kept emerging and re-emerge throughout history and caused an epidemic in the 18th century as industrial revolution significantly increased the population growth, widening the economic gap, increasing the number of populations living in slum areas. Expansion of slum area facilitates the transmission of TB, causing the increase of TB infection. Hence, driving the development of anti-TB. Streptomycin was the first successful treatment developed 60 years after MTB was discovered by Robert Koch (Keshavjee & Farmer, 2012). The success of Streptomycin led to other anti-TB agents such as Isoniazid, Rifampicin, and Pyrazinamide which are currently used as the standard treatment. The development of these antimicrobial agents was able to help gain control of TB.

As human evolves, bacteria also evolve to adapt to its environment. The increase usage of anti-TB drives the development of resistance towards such agents and it has become threats to human race. Up until now drug resistance TB is classified into multidrug resistance (MDR-TB), where patients show signs of resistance against Isoniazid and Rifampicin, and extreme drug resistance (XDR-TB), where signs of resistance also includes all fluoroquinolones and at least one injectable agent (Organization, 2015).

Despite the successful development of antibiotic, TB is still an international concern. Worldwide, it is estimated there was 9.6 million people with active case of TB and 1.2 million death to this disease in 2014. The case has grown up to 10 million active case and 1.4 million death in 2019 (Organization, 2015, 2020).

Indonesia is also unable to escape from the grasp of TB. It is estimated 32% of cases were underdiagnosed, and MDR-TB is common in Indonesia. The government has taken the issue seriously and conducted programs, collaborating with non-profit organization to eradicate TB. However, Indonesia is still ranked second in the world for TB (Kemenkes RI, 2019; Organization, 2015; Surya et al., 2017).

Hence, a study to understand TB patient journey is necessary to understand the complexity in eradicating TB in Indonesia. The biodesign method breaks down the complexity of healthcare to understand patient’s cycle of care from all stakeholder’s perspective. The finding in this study is expected to catalyze innovation for TB in Indonesia.

MATERIAL AND METHODS

The study is conducted using the Identify phase of biodesign method. It includes needs exploration, need statement development, and needs screening.

Need Exploration

Study utilized interview approach to collect data. Interviews were conducted to several key opinion leaders such as pulmonologist, non-profit organization, general practice doctors, and tuberculosis patient. Participants
were given full explanation of the research scope and required to sign an informed consent.

Interview questions were established according to the role of the interviewee and literature study found beforehand. There are several essentials’ elements to consider in formulating the questions.

**Need Statement Development & Analysis**

Insights from interview were formulated into needs. Needs statement were formulated in the structure: “A way to (problem) in (patient) that (outcome)”

Formulated needs went under preliminary filter. The filter is based on strategic focus which is built by assessing personal inventory by identifying personal passion, strength and weakness of each member and followed by aligning the mission that the team would like to achieve. The development of strategic focus also requires consideration towards the external factors. The essential external factor that must be considered is the opportunity areas. A deep understanding of the opportunity is achieved by gathering data and insight in various medical specialty these factors are formulated into acceptance criteria where each member of the group agrees to further process the need statements.

The remaining needs were analyzed based on DSTM analysis for screening purposes. DSTM analysis consist of four analysis which are Disease, Stakeholder, Treatment and Analysis.

Disease analysis aims to understand the impact of the medical condition towards the patients. Majorly focus on understanding the epidemiology, anatomy, physiology, pathophysiology, clinical presentation, clinical outcomes, and economic impact.

Stakeholder analysis identifies the importance parties/players involved in the healthcare ecosystem. Identification of the stakeholders is conducted by inspecting the cycle of care and cycle of money. Cycle of care provides the patient journey in the process of treating the disease, while cycle of money provides information on the movement of the cash flow in the cycle of care. Observation of these cycles also determines the extend of the influence of these stakeholders, whether it is influencer or hold the capacity to make decision.

Treatment analysis identifies the existing treatment and analyze the gap within the treatment. Factors to be observed are mechanism of action of the treatment,

Table 1. Essential elements in the interview

<table>
<thead>
<tr>
<th>Elements in Interview</th>
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<tbody>
<tr>
<td>1. Avoid binary question and use “why” to allow interviewee to elaborate his/her insights</td>
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<tr>
<td>2. Avoid the usage of “usually” while asking questions and ask about specific occurrence instead</td>
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<td>3. Encourage questions that leads to stories to understand interviewee’s point of view</td>
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<td>4. Search for inconsistencies as it may bring interesting insights</td>
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<td>5. Be aware of the non-verbal cues</td>
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<td>6. Allow a moment of silence when pause occur in an interview to provide the interviewee to reflect the answer given</td>
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<tr>
<td>7. Avoid suggesting answer to prevent unintentional agreement from the interviewee</td>
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<tr>
<td>8. Work in pairs or use voice recorded for complete proper documentation</td>
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</table>
emerging treatment, site and skills required to perform the treatment, and its cost. The analysis portrays the significance of developing a solution and to ensure that the proposed solution bridges the gap that the current treatments have.

Market analysis is utilized to understand whether the need is important in the population and viable for commercialization. Analysis begins by landscaping and segmenting the market to understand the total size of the need with its growth potential in commercialization and recognizing the current competitors in the market. Factors including the dynamics of the competition and willingness to pay. Upon target market identification, evaluation on each market segment in regards of the value if the need statement is addressed.

**Need Selection**

Upon the preliminary selection, the needs are further selected with constructive method. The selection uses pre-determined marking rubric. Rubric is designed following the important factors that are considered to be important, making sure to have taken into account all DSTM (Disease, Stakeholder, Treatment, and Analysis). The marking rubric used in this study uses the rubric in Biodesign (Zenios et al., 2009).

**RESULTS & DISCUSSION**

The data collected were formulated into needs statements (Table 2). Through the DSTM method, the needs that were considered as urgent are need statement 3, 8, and 9.

Through the accumulated needs statements, there are numerous factors contributes to the high susceptibility towards TB infection in Indonesia. It comes from the socioeconomics background, level of education, accessibility to healthcare service & role of government.

Study shows that majority people who are infected by TB are from the lower economic class, mainly living in the slum area. Due to poverty, they live in populous, damp, and poor ventilation housing (Kupat Kumis / Kumuh Padat Kumuh Miskin). The density of the population in the housing is increasing the risk of transmission of the bacteria if one of the residents is infected by TB.

**Tabel 2. Needs Statements upon Preliminary selection.**

<table>
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<tr>
<th>Need Statement</th>
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<tr>
<td>1</td>
<td>A way to address lack of awareness and education of TB in community that might be responsible for the spread and lack of precautionary measures.</td>
</tr>
<tr>
<td>2</td>
<td>A way to address active case finding in the community base, that still lacking and also contribute to the spread of TB</td>
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<tr>
<td>3</td>
<td><strong>A way to educate the population about early symptoms of tuberculosis to increase awareness and early infection detection</strong></td>
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<tr>
<td>4</td>
<td>A way to maintain tuberculosis program despite COVID-19 pandemic</td>
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<tr>
<td>5</td>
<td>A way to increase compliance on patient to consume prescribed medication completely and timely</td>
</tr>
<tr>
<td>6</td>
<td><strong>A way for easy, fast, affordable TB diagnosis in rural area</strong></td>
</tr>
<tr>
<td>7</td>
<td><strong>A way to improve BCG vaccine to provide immunity in adult population</strong></td>
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</tbody>
</table>

Need statement 3,6,7 are considered the top needs following the DSTM Analysis
In addition, poverty often comes hand in hand with lack of education. The lack of awareness and understanding of TB infection has become the major problem in Indonesia. Most people associate coughing blood with TB. However, it is not always the case. Persistent cough ongoing for more than 3 months is also a sign of TB infection. Such symptoms often considered as trivial matter, and believed to go away by itself, leading to the decision of not visiting a doctor to have it checked, causing the TB infection to be not diagnosed. Underdiagnosed patients do not have their TB treated and not taking any isolation measures, may unintentionally infect others.

Aside from that, there are challenges in treating diagnosed patients as well. The regiment of TB treatment requires regular intake of antibiotics and follow-up with physicians for several months, depending on the disease progression. The study shows that patients often stop taking the medication after the symptoms improve. Failure in following to comply with the given treatment not only prevent the complete clearance of the bacteria, but also gives the opportunity for the bacteria to develop resistance, commonly known as MDR-TB. There has been attempts to increase compliance in taking medicine, one of it is by setting up a team to remind patients about their medication (*Pengawas Minum Obat/PMO*). However, a cross sectional study concludes that PMO fails to increase compliance in patients. 66.6% patients were not reminded (Murtiwi, 2014).

Although the Indonesian government had setup a health coverage program (BPJS), and tuberculosis infection is fully covered, patients are still reluctant to pay a visit to physician. The BPJS coverage requires referral system where patient needs to go appointed public health center (Puskesmas) to receive referral for going to a bigger hospital. The current gold standard of TB diagnosis requires acquiring sputum from patient for lab analysis like bacterial culture and PCR-based testing. This diagnosis requires specific equipment and skilled laboratory technician. Hence, often this diagnostic service is only available in bigger hospital (i.e. less likely to be found in Puskesmas). The lack of access and long process to hospital with TB diagnostic services contribute to the underdiagnose of TB infection in Indonesia.

From socioeconomic perspective, as TB is closely correlated with lower economic class, there are many infected TB population whose earning is limited and unstable, causing them to be highly dependent on the daily income to survive for the day. Hence, taking part of their working time to visit hospital to receive referral and physician has become their last priority. This is because by visiting hospital, they are unable to work and hence will lose some income opportunity which may cause difficulty to survive through the day.

In addition, there is existing vaccine available to provide immunity towards MTB infection. It is bacilli Calmette-Guerin (BCG) vaccine. It has existed in the market for 80 years, and has become an essential in the national childhood immunization program. It is proven to be able to provide immunity against MTB in children. However, study shows variation in effectivity and diminished immunity in adulthood (Dockrell & Smith, 2017). It is worthwhile to dive deep into the MTB vaccine to investigate the potential to develop vaccine or vaccine booster to provide immunity against MTB in adulthood.

Due to the pandemic, the conducted study was highly relying on interview. Although interview provides in depth result, it is based the interviewee’s point of view. Opinion may be high on subjectivity and may not directly reflects the current condition. A better approach to reduce subjectivity is by observation study. By direct observation, clinical problems, populations, and desired
outcomes come to life and directly witnessed in the process. Recurring situations and issues can be observed and the evaluation in urgency can be measured, allowing the estimation of the opportunity. Ideally, researchers follow and observe interaction between patient with physicians in clinical settings. However, as the study was conducted during the COVID-19 pandemic, observation study was not conducted due to safety concerns.

Aside from limiting the study conducted, COVID-19 pandemic also causes difficulty in managing TB. This is because several symptoms of COVID-19 infection are cough, fever, and shortness of breath which is similar to TB infection. The similarity between these infection becomes a challenge in diagnosing whether a patient is infected by TB or COVID-19 (Akbar, Kahloun, Akbar, & Kahloun, 2020). Coinfection between TB and other respiratory infection, including COVID-19, leads to the rapid severe acute respiratory syndrome development. If the patient is also consuming immunosuppressive drugs, patient is at higher risk of TB infection or reactivation. Hence, it is expected that there will be a short-wave of TB pandemic after COVID-19 pandemic ends. There is the need to prepare for this upcoming surge to reduce the impact of TB pandemic in Indonesia (Crisan-Dabija et al., 2020; Yang & Lu, 2020).

CONCLUSION

Although Indonesian government and non-profit organizations have provided programs to help patients to manage, TB is still a challenge to eradicate. Attempts in regaining control over TB in Indonesia requires a full understanding on the healthcare system in TB management. The Biodesign approach discovered that the eradication of TB requires synergistic approach of incessant education on tuberculosis to raise awareness and increase diagnosis rate, improvement of healthcare access and facilities, and more straightforward less referrals in the reimbursement system. It is also valuable to explore the potential in developing TB vaccine with longer immunity or booster to prevent TB infection in adult.

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