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DISCUSSION AND FUTURE PERSPECTIVES

TB service can be portrayed as a chain of sequential factors, in which the strength of the chain is determined by its weakest link. This thesis presents the efforts to improve some of these weak links in the diagnosis and treatment of TB, as early diagnosis and effective treatment are essential in global TB control. Indeed, to end TB, a target set for 2035 by WHO [1], all factors in the TB service should work efficiently, flawlessly and simultaneously.

Delayed diagnosis of TB might explain why TB incidence has not declined more rapidly, despite the global scale-up of Directly Observed Treatment Short Course (DOTS). Considering that an estimated 3.4 million cases of tuberculosis remained undetected and unreported in 2017 [2], an effort to increase the detection and diagnosis of TB is urgently needed. In the Yogyakarta area alone, the case detection rate has only been 30.7% [Suharna, TB program manager of Yogyakarta Provincial Health Office, personal communication], and approximately 30% of active TB cases remain undetected at a national level by the Indonesian national health care system [3]. Earlier detection can prevent more advanced and severe forms of TB. It might reduce sequelae in survivors, improve overall survival rates and may prevent ongoing transmission by reducing the numbers of untreated active contagious TB patients in the community.

In high TB-burden and low and middle-income countries, the associated problems of stigma, neglect, low educational level, socio-economic barriers, and long travel distance to health facilities increase patient delay and undermine the global TB control effort. The notion of an Inverse Care Law – stating that available health care is inversely related to what is needed for the populations served – was first noted almost half a century ago, still applies today [4]. Earlier case finding using a rapid, point-of-care, easy to use instrument therefore would be an important asset. In our study, we found that the electronic nose generates modest diagnostic sensitivity (78%) and low specificity (43%) for the diagnosis of pulmonary TB. However, if approximately 78% of individuals with active TB were detected at the community level, the possibility to reduce undiagnosed TB in the community is nonetheless significant, especially if densely crowded communities with high TB incidence are targeted. Based on figures from the last TB incidence report [2], this test will improve findings by as many as 67,360 cases. Lower sensitivity might also be acceptable for technologies that increase case finding. Considering the severe health implications of TB, such an increase in case finding is clinically important. Furthermore, this test has higher sensitivity than symptoms screening (63% sensitivity in our data, or 70% sensitivity from a previous systematic review) [5]. With a further improvement of quality of the electronic nose, these results will even be better. In our meta-analysis, we found that the pooled sensitivity and specificity of electronic-nose in 6 previous studies were high, although these studies had moderate strength of evidence. As a point-of-care test, electronic-nose equipment conceptually provides results in a very short period of time at or near the location of the patient, thus the treatment plan can be adjusted according to the patients' need even before the patient leaves the health center or during a homecare visit. Apart from further improving the device, larger learning sets, *i.e.* true-positive group to show variety of true cases, may aid in improving sensitivity. The challenges in the future for novel diagnostic tools like breath test are to detect TB cases

with negative sputum smear, to determine specific VOCs in different stages of the disease, to investigate its accuracy in children, and to investigate its role in accelerating the diagnostic process at an affordable cost. Eventually, head-to-head comparisons with other screening instruments either based on exhaled breath, or other matrices and technologies, *e.g.* urine lipoarabinomannan detection tests [6,7], or PCR-based detection using tongue swabs [8] may lead to an improvement in TB screening in the community. Conceptually, various tests might even be combined as they might be complimentary.

While waiting for a point-of-care, fast, accurate, and easy-to-use TB diagnostic tool, we could improve case finding by mass campaigns, bill boards, sensitizing the community, with attempts to reduce stigma and increase outreach activities in areas with suspected high caseloads (*e.g.* slum areas with crowded living conditions and suspected high transmission). We observed that the diagnostic process based on the current work-up (using clinical evaluation, sputum smear microscopy, and chest radiography all together) in the Lung Clinics was highly precise (95.6% diagnoses were correct). Given that the diagnostic work-up following referral of an individual suspected to have TB was reliable, we considered that active case finding could be an important method to reduce the prevalence of active pulmonary TB in the community. This activity might importantly support TB control with a potentially large impact on TB transmission and incidence. It is critically important that while expanding reach-out, the health care team members are not only trained in the biomedical aspects of TB control, including personal protection measures, but also receive training in behavioural, psychological and cultural aspects. This should include stigma reduction [9], a compassionate and warm attitude, commitment and dedication to serve the victims of TB the best way possible, thereby reducing default and enhancing adherence to therapy [10].

Besides a prompt and correct diagnosis, another important link in the chain of effective tuberculosis control is the pharmacokinetic exposure to (1st-line) tuberculosis drugs. Indeed, previous studies have argued that perhaps low drug exposure in a minority of patients treated with 1st line TB drugs in fact results in monotherapy, and is a risk factor for drug resistance [11,12]. Selective antimicrobial pressure allows resistant mutants to repopulate lesions producing mono-resistance; if this process is repeated, multi-drug resistance ensues. Low TB drug exposure has also been associated with poor treatment outcome [12]. Many factors influence the bioavailability of any orally administered TB drug, such as body composition, comorbidities, genetic polymorphisms, malnutrition, pharmacokinetic drug-drug interactions, and concomitant food intake [13,14]. Besides host factors, also factors related to the offending *M. tuberculosis* isolate determine overall efficacy, especially if MIC is close to the breakpoint [15]. To achieve a successful treatment, an individual approach is required for patients who are prone to low drug exposure relative to the susceptibility of the *M. tuberculosis* isolate [11,16].

Therapeutic Drug Monitoring (TDM) has been proposed to improve treatment response in individual TB patients [17]. To implement this approach, an Optimal Sampling Strategy (OSS) may be used to reduce cost and time, and increase the feasibility and comfort for the patients.

In our study we developed an OSS for all first-line TB drugs in fasting and fed conditions, as well as intravenous administration, using multiple regression analysis. Future studies need to show the comparison of OSS development using other methods such as Bayesian analysis [18], as each method has its own advantages and disadvantages. Future studies are also required to address the development of OSS of first line TB drugs simultaneously in patients who may have risk factors for abnormal pharmacokinetics. One big challenge is to develop OSS with only two time points that are appropriate for all drugs in the treatment schedule that requires monitoring. It is conceivable that there needs to be some trade-off with slightly reduced optimal time points for some drugs in the schedule to safeguard the comfort of patients.

The last but not least important link discussed in this thesis is the innovation of treatment for TB. The inhalation route is much less challenging compared to other routes, such as the oral route, as solubility, dissolution rate, permeation through the membranes and bio-stability become less problematic [19]. Lower doses of drugs can be given because it avoids the first-pass metabolism and enables direct delivery to the lungs, and the drug concentration in the infected site of the lung might be high enough to overcome drug-resistant TB [20]. The inhalation route is also less invasive compared to the injection route. In addition, it may prevent drug-drug interactions which more likely happen in the systemic administration of multiple antibiotics [19]. Thus, it reduces systemic exposure and side effects, and eventually could optimize the fixed-dose combination therapy.

Inhaled particles need to overcome several barriers to achieve the desired pharmacodynamic effect, *i.e.* aerosol delivery, lung deposition, and clearance [21]. Many factors influence the success of inhalation therapies, not only the complex host-pathogen relationship, but also breathing pattern, patient's age, lung morphology and physiopathology [22]. Our small-sized proof of principle EBA study over 14 days found that the bactericidal activity of colistin sulphomethate sodium inhalation increased when it was combined with kanamycin i.v., even though in the two patients tested, it was still lower compared to the bactericidal activity of kanamycin i.v. alone. However, our study was not powered to draw any firm conclusions yet, as the case mix and chance effects of disease activity and sputum production over time are subject to naturally occurring fluctuations [23]. After our pilot study was completed, the WHO issued a rapid communication recommending discontinuation of kanamycin i.v. and capreomycin i.v., due to increased risk of treatment failure and relapse associated with their use in MDR-TB regimens [24]. A future well-powered and long-term study is planned to investigate further the EBA of colistin sulphomethate sodium DPI combined with another second bactericidal agent, or any of the current first choice agents used to combat MDR-TB. In theory, if colistin sulphomethate sodium and any of these drugs can work synergistically, the total dose of drugs might even be reduced.

In the rapid communication, WHO also recommended oral treatment for MDR-TB with novel and repurposed drugs, and limited the use of injectable agents [24]. The development of inhaled therapies will further improve safety and convenience of MDR-TB regimens. Once

developed successfully, it might become an option to replace the painful and more toxic intramuscular injection.

One of the challenges of inhalation therapy is to provide multiple anti-TB drugs in one inhaler device, as TB treatment always involves administration of multiple drugs. Another challenge is to enhance a peripheral deposition, as only one third of drugs was deposited in the peripheral lung, while the peripheral surface area is much larger than the upper airways or central airways [25]. The price of the inhaler would also need consideration, as high TB-burden countries usually are low or middle income countries, so that an effective but affordable inhaler technology is highly desirable.

To sum up, we believe that the diagnosis and treatment of pulmonary TB may be improved by using the inhalation route, *i.e.* breath test by an electronic nose, and administration of TB drugs by inhalation. While waiting for a point-of-care, fast, accurate, and easy-to-use TB diagnostic tool, we could incorporate active case finding and maximize the diagnosis by using clinical evaluation, sputum smear microscopy, and chest radiography all together to reduce the prevalence of active pulmonary TB in the community. Tailoring TB treatment to individual needs is another important aspect, because many factors influence the drug exposure, which eventually change the treatment outcome. For this, an OSS can be a useful tool in therapeutic drug monitoring to adjust the drug dosage according to individual needs. Eventually, with correct diagnosis and treatment, patient care will be optimized; this should result to help end TB in our life time.

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