Collaborative TB research between Universitas Padjadjaran and Radboudumc
TB clinic, Jakarta 1998
Bandung TB working group

Aims

• internationally credible and relevant research
• impact on quality of TB prevention and care in Indonesia
• research capacity (institutional and individual)
Patient related research

sick people who might have TB
\[\rightarrow\]
diagnostics
\[\rightarrow\]
TB patients
\[\rightarrow\]
antibiotic treatment
\[\rightarrow\]
cure

healthy controls

genetic susceptibility

Ida Parwati

Bachti Alisjahbana

Nina Ruslami
What factors drive these steps?

Exposure to an infectious TB patient

Latent tuberculosis infection

Active TB disease

(treatment) outcome

How to improve patient outcome and control of TB at population level?

How do we study this?

How do we have impact?
What drives this?
- Social factors
- *Mtb* virulence
- Host defence
- Co-morbidity
- Drug resistance
- Health systems factors
- ..

To help pts & control TB
- vaccination
- better diagnosis
- Better drug treatment
- Deal with resistance
- manage co-morbidity
- Addressing gaps in ‘cascade of care’
- Host-directed therapy
- ..

Having impact
- Writing papers
- Better guidelines
- Education
- Dissemination
- Engagement
- stakeholders
- ..

How do we study this?
- Patient cohorts
- Diagnostic studies
- Lab sciences
- Clinical trials
- Epidemiology
- public health studies
- ..
Collaborative international PhDs

2007

Tuberculosis
in Indonesia:
Host Response
and Patient Care

Optimizing Drug Interventions in the fight against tuberculosis

Factors Underlying the Success of the Mycobacterium tuberculosis Beijing Genotype in Indonesia

Management of children living with tuberculosis patients: impact on treatment

Etiology and Clinical Management of Adult Meningitis in Indonesia

2019

Understanding the Dynamics of Tuberculosis Drug Resistance, Disease Phenotype and Transmission by Multilocus Genotypic Analysis

Tuberculosis Diagnosis and Genotyping in Indonesia

Host response in relation to tuberculosis susceptibility, transmission and outcome

Macrolide Resistance between Multidrug Resistant Tuberculosis Clones

Collaborative international PhDs
International PhD theses, ongoing

Valerie Koeken  
immunology of tuberculosis

Intan Mauli  
immunology aspergillosis

Annisa Rahmalia  
HIV and women

Bony W Lestari  
TB health systems performance

Raspati Koesoemadinata  
TB and diabetes

Edwin Ardisinyah  
‘omics’ tuberculous meningitis

Ajie Mandala  
functional genomics of diabetes

Todia Setiabudiwan  
innate immunity to \textit{Mtb} infection
Today (3 PhD students)

• What is a patient’s journey to be diagnosed and treated for TB in Indonesia?
• How can we screen and manage diabetes-associated TB?
• How can we understand why some people develop really severe TB and die?
What is a TB patient’s journey to be diagnosed and treated in Indonesia?

Graduated in 2000 as medical doctor from Universitas Padjadjaran

2000-2007: Working as GP in Community Health Center, Garut, West Java

2010: Graduated from NIHES-Erasmus University Rotterdam, specialization clinical epidemiology

2010-2017: Working as public health researcher at Infectious Disease Research Center, UNPAD

2017 – now: doing PhD at Radboud Institute for Health Sciences, supervised by Prof. Reinout van Crevel

Bony Wiem Lestari
TB in Indonesia

- 260 million people
- 3rd highest TB burden globally
- Incidence: 391/100,000
- HIV: 4.4%
- Diabetes: 13%
- Multidrug resistant (MDR)-TB:
  - 2.8% in new TB cases
  - 16% in previously treated cases
Health system in Indonesia

Private Sector

- Private Clinic
- Secondary Private Hospital
- Tertiary Private Hospital

Public Sector

- Primary Health Center
- Secondary Public Hospital
- Tertiary Public Hospital

Horizontal referral

TB program within Indonesian Health System

Vertical referral
Private sector and TB:
- 60% of outpatient care
- 43% of hospital admissions

The private sector contributed only 9% to the notified TB cases in 2015.

Research questions:

What is the patient pathway to TB diagnosis and treatment? What type of healthcare providers do they meet?

Where are TB diagnosed and treatment started? What is the time to TB diagnosis and treatment?

What factors are associated with delay diagnosis and treatment?
Methods

- Cross-sectional study in an urban setting: Bandung – West Java, Indonesia
- Recruited adults with newly diagnosed TB (1 October 2017 to 31 January 2019). In-person interview
- From CHC, hospital and private practice
- Questionnaire adapted from the “Tool to estimate patient costs”
- Analysis:
  - Descriptive stats.
  - Adjusted odds ratios using logistic regression
Question to you

Where do most TB patients go first when they have symptoms?

1. community health center
2. Public Hospital
3. Private doctor
4. Private hospital
5. Informal provider
Pathways undertaken by tuberculosis patients for diagnosis and treatment in Bandung (N=401)

L0 = informal providers (pharmacy, drug sellers, drug store, etc.); L1a = Community Health Center; L1b = private practitioner or private clinic; L2a = public hospital; L2b = private hospital.

*Lestari, et al. Patient pathways and delays to diagnosis and treatment of TB in an urban setting in Indonesia. Accepted for publication, The Lancet Regional Health Western Pacific, Nov 2020*
Question to you

How many visits to health professionals does I take on average to reach a TB diagnosis?

1. 2
2. 3
3. 4
4. 6
5. More than 6
Proportion of patients diagnosed, or with a missed diagnosis, over sequential visits, stratified by recruitment site

Median number of visits until TB diagnosis = 6

Lestari, et al. Patient pathways and delays to diagnosis and treatment of TB in an urban setting in Indonesia. Accepted for publication, The Lancet Regional Health Western Pacific, Nov 2020
Time to TB diagnosis and treatment

Onset of TB symptoms

Initial presentation to healthcare provider

TB Diagnosis

TB Treatment

Patient delay 30 days

Diagnostic delay 23 days

Treatment delay 1 day

Total delay 65 days

Health system delay 28 days

62 days

Number represents the median

Risk factors for delays

- **Onset of TB symptoms**
  - Male: aOR 1.6
  - Lower education: aOR 1.9
  - No health insurance: aOR 2.1

- **Initial presentation to healthcare provider**
  - No health insurance: aOR 1.9
  - Multiple HCP visits: aOR 12.4
  - Initial visit to private practitioner: aOR 2.6

- **TB Diagnosis**
  - Multiple HCP visits: aOR 2.2
  - Being diagnosed by a private practitioner: aOR 5.7

- **TB Treatment**

---

Lestari, et al. Patient pathways and delays to diagnosis and treatment of TB in an urban setting in Indonesia. Accepted for publication, The Lancet Regional Health Western Pacific, Nov 2020
Summary

Conclusions

- Patient pathways in Indonesia are complex, involving the public and private sector, with multiple visits and long delays, especially to diagnosis.

- A widely available accurate diagnostic test for TB could have a dramatic effect on reducing delays, onward transmission and mortality.

Recommendations

- Strengthening of public and private sectors

- Increase universal health insurance coverage

- Access to better diagnostic tools

Winner – November 2020
<table>
<thead>
<tr>
<th>Year</th>
<th>Study/Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-2004</td>
<td>Medical Doctor; Faculty of Medicine Universitas Padjadjaran</td>
</tr>
<tr>
<td>2004-2006</td>
<td>GP; Bandung District, West Java</td>
</tr>
<tr>
<td>2006-2008</td>
<td>PTT (remote area); Ketapang, West Kalimantan</td>
</tr>
<tr>
<td>2009-2012</td>
<td>Research Assistant; Tuberculosis Working Group, UNPAD</td>
</tr>
<tr>
<td>2013-2017</td>
<td>MSc Epidemiology by distance learning; London School of Hygiene and Tropical Medicine, UK</td>
</tr>
<tr>
<td>2013-now</td>
<td>Research Manager; Tuberculosis Working Group, UNPAD</td>
</tr>
<tr>
<td>2017-now</td>
<td>PhD student by sandwich programme; Radboud University Medical Center, Nijmegen, The Netherlands</td>
</tr>
</tbody>
</table>
What is the most important risk factor for TB?

A. Smoking
B. HIV
C. Poverty
D. Diabetes
E. All correct
Tuberculosis and diabetes mellitus

- 10.4 million TB cases
- 1/4 world latently infected
- 1.7 million deaths, 95% in LMIC

- 425 million with DM, 50% undiagnosed
- >90% Type II
- 80% living in LMIC
- Increase to 630 million by 2045
- 4 million deaths annually

Estimated TB incidence 2016

Estimated DM prevalence 2017
Median 30 yrs, 
1.5% HIV+ 
13.5% **DM** (70% new DM) 
(3.2% of controls; OR 4.7)

*Alisjahbana et al, Int J Tuberc Lung Dis 2006*
DM is associated with active TB

- 44 studies from 16 countries
- Prospective: DM ~ 3.6-fold higher TB risk (2.3-5.7)
- Higher in low-income and high-incidence
- Higher in Asia compared to Europe/USA
- Higher for confirmed TB and blood tested DM
- DM accounts for 11% (Nigeria) to 18% (India) of TB in high burden countries

Al-Rifai, Pearson, Critchley, Abu-Raddad. Plos One 2017
What are the effects of DM on TB?

A. More TB transmission (more latent TB)
B. More active TB
C. More lung cavities
D. More drug resistance
E. More TB outside the lungs
F. More TB deaths
G. More recurrent TB
H. All of the above
TANDEM: understanding diabetes and TB

“The TANDEM Consortium brings together partners with complementary skills in clinical studies, epidemiology, health economics, human genetics and immunology.”

Lancet Diabetes Endocrinology, 2014
How to manage DM in a patient with active TB?

• Glycemic control during TB treatment is important, but challenging:
  • TB-associated inflammation
  • drug-drug interaction
  • programmatic issue
• Current guideline in Indonesia: Insulin for severe infection such as TB → insulin is not widely available
• Referral to a DM clinic → undesirable (transmission in DM clinic, patient refusal)
• As a result: many TB-DM patients are inadequately treated
• Hypothesis: Intensified counselling, blood glucose monitoring, and DM medication adjustment during TB treatment can improve glycemic control
Study design

- **Primary endpoint:** change from baseline HbA1c, 6 months after TB treatment
- **Secondary endpoints:** safety

**Study Design Flowchart:**

1. **Patients with DM** → Bi-directional screening & baseline examination → DM patients → Randomization → Intervention arm
2. **Patients with TB** → Bi-directional screening & baseline examination → TB-DM patients → Randomization → Control arm
3. TB patients → Bi-directional screening & baseline examination → Safety

Followed up for 6 months:
- HbA1c examination at month 0, 3, and 6
- Physical exam, CXR, sputum test at month 0, 2 and 6
Structured algorithm

Three components:
- More frequent glucose measurement
- Adjustment of medication based on glucose levels with simple algorithms
- Counselling and education about TB and DM
Algorithm for adjusting medication

Flowchart A: metformin
Flowchart B: metformin + basal insulin
Flowchart C: basal insulin + rapid-acting insulin
Flowchart D: refused insulin → Metformin + other oral anti DM (sulphonyl urea)
# Counselling and education

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>TB: cause, transmission, treatment compliance, possible side effects.</td>
</tr>
<tr>
<td>2.</td>
<td>DM: what is DM? What are the symptoms? What can be done?</td>
</tr>
<tr>
<td>3.</td>
<td>Glucose measurement and recording.</td>
</tr>
<tr>
<td>4.</td>
<td>Importance of glycemic control.</td>
</tr>
<tr>
<td>5.</td>
<td>Metformin and insulin (use, precautions, side effects).</td>
</tr>
<tr>
<td>6.</td>
<td>Hyperglycemia and hypoglycemia.</td>
</tr>
<tr>
<td>7.</td>
<td>The importance of smoking cessation for both TB and DM.</td>
</tr>
<tr>
<td>8.</td>
<td>DM and TB together – more difficult to treat.</td>
</tr>
<tr>
<td>10.</td>
<td>Management after TB treatment is completed</td>
</tr>
</tbody>
</table>
Results

Patients with TB and DM (n=218)

Excluded (n=55)*, refused (n=11), Not randomized for unknown reason (n=2)

Patients TB-DM randomized (n=150)

Intensive arm (n=76)

Died (n=2)
Dropped out TB therapy (n=3)
Moved to another city (n=2)
Became MDR-TB (n=1)

Completed follow up (n=68)

Control arm (n=74)

Did not wish to continue (n=2)
Dropped out TB therapy (n=5)
Moved to another city (n=1)

Completed follow up (n=66)
Proportion with HbA1c<8%

- **Month 3**
  - Control arm: 11.6 (SD: 2.5)
  - Intervention arm: 9.7 (SD: 2.7)

- **Month 6**
  - Control arm: 9.8 (SD: 3.3)
  - Intervention arm: 7.6 (SD: 1.6)

**P-value**
- Month 3: 0.035
- Month 6: 0.001
## Table 6.3: Management of HbA1c or blood glucose at the start of TB treatment

<table>
<thead>
<tr>
<th>HbA1c or FBG at the start of TB treatment</th>
<th>TB patient diagnosed with new DM</th>
<th>TB patient already receiving treatment for DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HbA1c &lt;8% or FBG &lt;10.0 mmol/l (180 mg/dl)</td>
<td>No further immediate action is taken; re-assess blood glucose levels at 2 months and again at the end of TB treatment</td>
<td>No further action is taken; the patient continues on current medication for DM</td>
</tr>
<tr>
<td>If HbA1c ≥8% but less than 10% or FBG ≥10 mmol/l (180 mg/dl) but less than 15 mmol/l (270 mg/dl)</td>
<td>Start metformin 500 mg once a day, reassess in two weeks and increase the dose to 500 mg twice a day or refer if blood glucose levels have not improved</td>
<td>Intensify current glucose-lowering treatment and reassess one–two weeks later</td>
</tr>
<tr>
<td>If HbA1c ≥10% or FBG ≥15 mmol/l (270 mg/dl)</td>
<td>Start metformin 500 mg twice a day and seek specialist advice</td>
<td>Seek specialist advice and consider the need for hospital admission for better glucose control</td>
</tr>
</tbody>
</table>
Conclusion

• DM in TB poorly controlled.

• Simple algorithm can help glycemic control in TB clinic (in scientific study)

• Implementation under routine conditions may be difficult.

Recommendations

• Need to screen TB patients for DM and vice versa.

• Need for clinical algorithms for TB-DM management

• Larger studies needed to evaluate best approach and associate costs.
Our other research questions on TB-DM

• What is the prevalence of TB in DM patients and vice versa?
• How to best screen TB patients for DM and vice versa?
• What is the prevalence of latent TB in DM patients?
• What is the incidence rate of TB in DM patients?
Acknowledgement

- **UNPAD Bandung, Indonesia**: Bachti Alisjahbana, Rovina Ruslami, Nanny NM Soetedjo, Prayudi Santoso, Lidya Chaidir

- **UO Dunedin, New Zealand**: Philip Hill, Sue McAllister

- **SGUL London, UK**: Julia Critchley, Sarah Kerry, Fiona Pearson

- **LSHTM London, UK**: Hazel Dockrell, Dave Moore, Ulla Griffiths, Daniel Grint, Yoko Laurence, Jacqueline Cliff, Clare Eckold

- **RUMC Nijmegen, Netherlands**: Reinout van Crevel, Mihai Netea, Rob Aarnoutse, Lindsey te Brake, Ekta Lachmandas
# Tuberculous Meningitis

**Edwin Ardiansyah**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study/Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-2010</td>
<td>Medical Doctor; Faculty of Medicine Universitas Padjadjaran</td>
</tr>
<tr>
<td>2011-2014</td>
<td>GP; Cianjur and Bandung, West Java</td>
</tr>
<tr>
<td>2014-2015</td>
<td>Research Assistant; Avian influenza study – Unpad</td>
</tr>
<tr>
<td>2016-2018</td>
<td>Msc. Medical Biology, Radboud University</td>
</tr>
<tr>
<td>2019-now</td>
<td>PhD student, RadboudUMC Nijmegen, the Netherlands ‘omics’ of TB meningitis</td>
</tr>
</tbody>
</table>
TB Meningitis..

Most severe form of TB
Often in small children and immunocompromised (HIV)
High mortality (~30% in-hospital, ~50% after 6 months)

Long history of studies in TB meningitis UNPAD-Radboud
Damaging inflammation (‘collateral damage’)

Inflammation  hydrocephalus  Pseudo-abscess  infarction

MRIs from Bandung, thanks to:
Robby Hermawan / Sofiati Dian
Question

Amongst people infected with TB, what is the proportion of people getting TB meningitis?

a) 1-2%
b) 5-10%
c) 10-20%
Body temperature

CSF: blood glucose ratio

CSF neutrophils

Blood neutrophils

Arjan van Laarhoven, Sofiati Dian et al, J Inf Dis 2017
corticosteroids for TB meningitis

- RCT Vietnam, dexamethason (n=545), *New Engl J 2004*
- Decreased mortality (30%), especially for mild cases
- No effects on neurological sequelae
- Waning effect over time

*Torok, Plos One 2011*
What biological pathway to target?

- unbiased approach integrating ‘omics’
- patient cohort Bandung
- prospective follow-up (survivors, versus non-survivors)
- controls: lumbar puncture, no TB, no meningitis

- archived CSF and plasma
- metabolomics = products of cellular metabolism (glucose, lactate, amino acids, fatty acids..)

- integration with genome-wide SNP-typing
Cerebrospinal fluid (CSF)

Comparison between:
- Patients who died
- Patients who survived
- Controls without meningitis

Products of cellular metabolism:
- Glucose
- Lactic acid
- Amino acids
- Fatty acids
- ...

Arjan van Laarhoven
Survivors versus nonsurvivors

higher in survivors
higher in nonsurvivors

ratio nonsurvivor / survivor
unadjusted p-value

CSF_outcome_logFC_alpha

ratio survivor / control

CSF_outcome_logFC_color

CSF/serum albumin ratio (r)

m/z

LTB4

glucose

tryptophan
CSF tryptophan predicts mortality

discovery cohort
N = 55

validation cohort
N = 124

mortality ~

CSF tryptophan (μmol/L):

< 0.18

0.18-0.66

> 0.66

p < 10^{-7}

van Laarhoven et al. Lancet Infectious Diseases 2018
Why would tryptophan be relevant?

1. Macrophage tryptophan is nutrient for mycobacteria

2. Tryptophan metabolites skew T-cell immunity

3. Tryptophan metabolites: neuroprotective and neurotoxic
Tryptophan metabolism and TB. Tryptophan is metabolized via multiple pathways (Figure 2), of which the kynurenine pathway is of particular interest. IDO1 is upregulated in TB, leading to the accumulation of kynurenic acid, which is neuroprotective. 5-HIAA is a metabolite of serotonin and is elevated in TB. The figure shows the metabolic pathways involving tryptophan, including the production of L-serotonin, L-kynurenine, and 5-HIAA. The figure also highlights the involvement of the aryl hydrocarbon receptor (Ahr) in the metabolic pathways. Further studies are needed to understand the role of these pathways in TB.
Can we support this with genetics?

- unbiased (instead of candidate, e.g. gene encoding for enzyme IDO1)
- Genome-wide SNP typing (~400,000 SNPs, common variants)
- Imputation from reference genomes ~ 6,000,000 SNPs
  (remember: 20-25,000 genes; >3 billion basepairs)
- Quantitative instead of binary trait

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>GT</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>TT</td>
<td>58</td>
<td>22</td>
</tr>
</tbody>
</table>

Calculate $\chi^2$ statistics

**Binary trait**

**Continuous trait (QTL)**
Genetics predict CSF tryptophan (n=130)

Genetic risk score (Tryptophan QTLs) \sim higher mortality
Other metabolites ~ mortality TB meningitis?

193 metabolites significantly different (corrected for multiple testing)

29 annotated
164 un-annotated

‘annotated’ (known)

‘unannotated’ (unknown)
The ULTIMATE project

2100 HIV+/HIV- patients
Vietnam & Indonesia *

Detailed clinical data
and brain MRI

CSF / blood transcriptomics

CSF / blood metabolomics

Integrative analysis

patient DNA genotyping

* Including pts randomized to steroids or placebo

“Using tryptophan metabolism and response to corticosteroids to define new therapeutic target for TB meningitis”

Vietnam and Indonesian cohorts/RCTs combined (N=2100). Funding from NIH
## Whole genome sequencing (WGS) instead of SNP-typing

<table>
<thead>
<tr>
<th>Chromosomes</th>
<th>SNP (n)</th>
<th>MAF&lt;0.05 (%)</th>
<th>MAF&lt;0.01 (%)</th>
<th>Not annotated in dbSNP (SNP database)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>MAF&gt;0.05 (%)</td>
<td>MAF&lt;0.05 (%)</td>
</tr>
<tr>
<td>1</td>
<td>975598</td>
<td>560871 (57.49)</td>
<td>394189 (40.4)</td>
<td>119255 (12.22)</td>
</tr>
<tr>
<td>2</td>
<td>1033119</td>
<td>610279 (59.07)</td>
<td>426544 (41.29)</td>
<td>112816 (12.72)</td>
</tr>
<tr>
<td>3</td>
<td>887113</td>
<td>516651 (58.24)</td>
<td>363699 (41)</td>
<td>103994 (11.79)</td>
</tr>
<tr>
<td>4</td>
<td>881929</td>
<td>494317 (56.05)</td>
<td>342418 (38.83)</td>
<td>103994 (11.79)</td>
</tr>
<tr>
<td>5</td>
<td>792504</td>
<td>459146 (57.94)</td>
<td>322321 (40.67)</td>
<td>102008 (12.87)</td>
</tr>
<tr>
<td>6</td>
<td>769101</td>
<td>442946 (57.59)</td>
<td>306854 (39.9)</td>
<td>93126 (12.11)</td>
</tr>
<tr>
<td>7</td>
<td>722165</td>
<td>407139 (56.38)</td>
<td>283054 (39.2)</td>
<td>87571 (12.13)</td>
</tr>
<tr>
<td>8</td>
<td>672982</td>
<td>387379 (57.56)</td>
<td>274836 (40.84)</td>
<td>82804 (12.47)</td>
</tr>
<tr>
<td>9</td>
<td>533786</td>
<td>303498 (56.86)</td>
<td>211814 (39.68)</td>
<td>79 (11.87)</td>
</tr>
<tr>
<td>10</td>
<td>617352</td>
<td>351791 (56.98)</td>
<td>246234 (39.89)</td>
<td>48 (11.31)</td>
</tr>
<tr>
<td>11</td>
<td>611787</td>
<td>355765 (58.15)</td>
<td>256110 (41.86)</td>
<td>66 (11.93)</td>
</tr>
<tr>
<td>12</td>
<td>595285</td>
<td>343668 (57.73)</td>
<td>239629 (40.25)</td>
<td>10 (11.69)</td>
</tr>
<tr>
<td>13</td>
<td>458224</td>
<td>267506 (58.38)</td>
<td>188093 (41.05)</td>
<td>79 (11.69)</td>
</tr>
<tr>
<td>14</td>
<td>410337</td>
<td>239469 (58.36)</td>
<td>167916 (40.92)</td>
<td>44 (11.49)</td>
</tr>
<tr>
<td>15</td>
<td>364280</td>
<td>211870 (58.16)</td>
<td>146504 (40.22)</td>
<td>36 (11.46)</td>
</tr>
<tr>
<td>16</td>
<td>390807</td>
<td>223444 (57.18)</td>
<td>158456 (40.55)</td>
<td>85 (11.72)</td>
</tr>
<tr>
<td>17</td>
<td>338737</td>
<td>197298 (58.25)</td>
<td>139193 (41.09)</td>
<td>81 (11.89)</td>
</tr>
<tr>
<td>18</td>
<td>349959</td>
<td>202281 (57.8)</td>
<td>140190 (40.06)</td>
<td>11 (11.38)</td>
</tr>
<tr>
<td>19</td>
<td>282371</td>
<td>158561 (56.15)</td>
<td>106926 (37.87)</td>
<td>57 (10.43)</td>
</tr>
<tr>
<td>20</td>
<td>272129</td>
<td>156880 (57.65)</td>
<td>111112 (40.83)</td>
<td>43 (11.59)</td>
</tr>
<tr>
<td>21</td>
<td>175468</td>
<td>96626 (55.07)</td>
<td>68785 (39.2)</td>
<td>18570 (10.87)</td>
</tr>
<tr>
<td>22</td>
<td>170911</td>
<td>99127 (58)</td>
<td>67163 (39.3)</td>
<td>1498075 (12.17)</td>
</tr>
</tbody>
</table>

### Diagram

- **Strength of effect**:
  - Rare genetic variants with strong effect
  - Common variants with modest effect
- **Allele frequency**:
  - WGS
  - SNP typing
- **Not annotated in dbSNP (SNP database)**:
  - MAF>0.05 (%)
  - MAF<0.05 (%)
  - MAF<0.01 (%)
WGS to improve imputation

WGS of 113 Indonesian HIV-neg TBM pts & 1000 Genomes Project

Indonesian genetic architecture is unique compared to the East-Asian population.
Conclusion

• Omics provide insight into biological pathway involved in immunopathology TB
• Cerebral tryptophan metabolism linked to mortality TB meningitis; many other possible biological pathways
• Whole genome sequencing: rare variants with strong effects & better imputation
• All this to help develop host-directed therapy for TB
Summary today

• What is a patient’s journey to be diagnosed and treated for TB in Indonesia?
• How can we screen and manage diabetes-associated TB?
• How can we understand why some people develop really severe TB and die?
• What has helped to make this collaboration a success?
Strengths of this academic collaboration

- Comprehensive approach (molecule – patient – population)
- Multidisciplinarity
- Talent management
- Well-embedded (community, hospitals & policy makers)
- Longstanding international collaboration
- Strong leadership & strong values
Thank you

A. Rizal Ganiem
Nina Ruslami
Bachti Alisjahbana
Lidya Chaidir
Sofiati Dian

Todia Setiabudiwan
Raspati Koesoemadinata
Bony W Lestari
Jakko van Ingen
Lindsey te Brake

Valerie Koeken
Edwin Ardiansyah
Arjan van Laarhoven
Mihai Netea
Vinod Kumar
Rob Aarnoutse

National Institute of Health
European Commission
Broad Institute, MIT, Harvard
Universitas Padjadjaran
Radboud University
Oxford University