OS1-1

Comparative genetic variation of DosR-related genes among Mycobacterium tuberculosis lineages

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Mycobacterium tuberculosis (MTB) is a dreadful human pathogen. MTB shift from replicating to non-replicating with low metabolic activity during latency state. Dormancy survival regulator (DosR) regulon is essential for adaptation to these conditions. At least 48 genes were considered to be members of DosR-regulon as their gene expression were induced by dosR regulator. To analyze genetic polymorphism of 48 genes in *dos*R-regulon among 1,184 clinical isolates *M. tuberculosis* compared to reference strain H37Rv. Whole genome sequencing of clinical MTB isolates was done by using illumina Hiseq, then variant calling was performed by GATK program. Among 48 *dos*R-regulated genes, a total of 18,123 substitutions were called, corresponding to 1,053 SNPs and indels loci. Of these SNPs and indels, 876 (83.2%) were coding region SNPs and indels, thus 580 nonsynonymous substitution (66%) were identified. Furthermore, 66 SNPs and indels loci were lineage-specific SNP. Lineage 1 or EAI had the highest SNPs frequency per lineage identified in *dos*R-regulon compared to other MTB lineages, especially the *dos*R-regulated genes involving in stress protein, latency antigen and membrane protein. Therefore, functional consequences of genetic variation among *dos*R-related genes will be further explored.

OS1-2

GWASs functional variants with tuberculosis susceptibility in the Han Chinese population

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Background: How GWAS associated variants involved in the pathogenesis of TB were not well elucidated.

Methods: Five TB GWAS single nucleotide polymorphisms (SNPs) in gene region were enrolled and evaluated among 764 pulmonary TB patients and 764 healthy controls.

Results: The GA genotype of rs1418267 significantly decreased the risk of TB by 0.37 fold (95%CI, 0.49-0.81, $P_{Bonferroni}$=0.0012). Based on the IGRA results, GA genotype of rs1418267 was found in association with a statistically significant decreased risk of TB among TB cases and IGRA negative controls ($P_{Bonferroni}$=0.003). The mutant homozygote AA of SNP rs4733781 significantly decreased the risk TB by 0.42 fold (95%CI, 0.43-0.79, $P_{Bonferroni}$=0.0015) and the homozygote AA of rs4733781 showed a statistically significant decreased risk on TB by 0.44 fold among TB cases and IGRA negative controls (95%CI, 0.40-0.77, $P_{Bonferroni}$=0.0012). ERP44 and ASAP1 expression were not found differentially expressed among the genotypes of each SNP (P=0.512 for rs1418267, P=0.269 for rs4733781).

Conclusions: SNPs rs1418267 and rs4733781 were associated with decreased risk of TB in Han Chinese population, and other genes might be modulated by the disease associated variants. Meanwhile, genes expression in different stages prior to TB disease are needed to evaluate in further studies.

OS1-3

Comparisons of Mycobacterium tuberculosis drug susceptibility based on the whole genome sequences with phenotypic drug resistance in Thailand

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Detection of drug-resistant *M. tuberculosis* is needed for effective treatment and control of tuberculosis. Conventional phenotypic susceptibility testing is time-consuming method, requiring 4-6 weeks until reporting the result. In this study we demonstrated the use of whole genome sequencing (WGS) for prediction of the first-line anti-TB drug resistance phenotype. A total of 1184 *M. tuberculosis* strains isolated from Chiang Rai Province, Thailand, were whole-genome sequenced. Forty-one reported resistance genes, consisting of 26, 3, 4, and 8 genes for isoniazid, rifampicin, streptomycin, and ethambutol resistance, respectively, were investigated. Resistance-associated mutations were identified based on our own knowledge and published databases. Comparison with standard drug susceptibility testing WGS showed sensitivity and specificity of 92.4% and 99.6% for rifampicin, 93.9% and 98.5% for isoniazid, 83.3% and 98.9% for streptomycin, and of 66.7% and 97.9% for ethambutol. False negative mostly came from uncharacterized or unknown resistance mechanisms. Prediction of resistant phenotype using WGS showed promising results for rifampicin, isoniazid, and streptomycin but showed low sensitivity for prediction of ethambutol resistance. However, advanced knowledge of resistance mechanisms and collection of susceptible mutations could help to improve the accuracy of the test, making it as a method of choice for TB diagnosis.

OS1-4

Pilot study of development of EQA program for molecular technique of Mycobacterium tuberculosis in Thailand

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Molecular technique is a rapid and efficient tool diagnosis for detection of MTB from clinical specimen. In Thailand this technique has been increasingly used for diagnosis MTB but lack of EQA for maintain the quality of processing. EQA is one of major mechanism to ensure the quality of laboratory performance including microscopy, culture and DST but not for TB molecular technique. Therefore, National TB Reference Laboratory has developed and prepared DNA sample for using in EQA of TB molecular test in Thailand. The dead TB bacilli were used and extracted DNA from them and put in the tube and dry. Five difference strains of organism including MTB, NTM and other bacteria were used in this study. Each strain was prepared 100 tubes of DNA and then random for 60 tubes, 30 tubes were performed by real time PCR, Xpert MTB/RIF and the remain 30 tubes were perform by LPA technique, GenotypeMTBDRplus.The result showed that 97% and 100% in comparable with standard by using Xpert and GenotypeMTBDRplus test, respectively. The mass production of DNA sample can prepare according to this pilot method and can implement to all laboratories in country where perform molecular test for MTB.

OS1-5

Household catastrophic expenditure for tuberculosis care and its determinants after the implementation of universal health coverage in Indonesia

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Introduction

While households affected by TB remain struggling to cover TB-related costs that may cause catastrophic expenditure, universal health coverage (UHC) implemented in Indonesia may reduce costs incurred beyond treatment costs.

Method

This cross sectional study interviewed adult patients receiving pulmonary, sensitive TB drugs treatment in Indonesia during 2016. We measured all type of costs before and after diagnosed as TB using validated questionnaire and household catastrophic expenditure using the threshold of $\geq$40%, $\geq$25% and $\geq$15%. We used a logistic regression to analyze its determinants.

Results

This study interviewed 246 subjects in urban (32.9%), sub-urban (27.6%) and rural (39.4%) areas. Many households were still uncovered by health insurance (40.7%) and should cope with high costs by borrowing money (34.6%) and selling property (12.4%). Average pre-diagnostic and diagnostic costs for TB were US$ 21.57 and were significantly related to catastrophic spending. The incidence of household facing catastrophic expenditure was 8.1%, 14.2% and 23.6%, using threshold of $\geq$40%, $\geq$25% and $\geq$15% respectively; and determined by female gender (aOR 7.3; 95% CI, 2.2, 24.7), rural residence (aOR 4.8; CI 0.9, 23.8), and first contact to private facility (aOR 3.8; CI 1.2, 11.9).

Conclusion

Implementation of UHC is still not enough to prevent catastrophic expenditure because of pre-diagnostic and diagnostic costs which are majorly still uncovered. The government should provide more publicly-linked care that can be accessed freely, especially in rural area.

OS2-1

Remote Smearing Station/Smearers at GIDA (Geographically Isolated Disadvantage Areas) and far flung barangays)

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The establishment of the Remote Smearing Station at Geographically Isolated Disadvantaged Areas (GIDA) of the Municipality of Payao has been helping a lot of TB patients get the diagnosis with minimal coast, time and effort going to the poblacion and riding a habal-habal for almost 1-1 1/2 hour. The site which was well-supported by the Barangay Captain, has been serving the community through readily accessible Sputum Smear Services that only takes 3-4 hours (for good quality specimen) before release of result and eventually, enrollment of patient for treatment. The Station is operated by equipped and trained Informal Laboratory Workers trained by the DOH Regional Office IX who function to collect sputum sample from persons manifesting signs and symptoms of Tuberculosis, perform smearing and fixation and refer smeared slides to the microscopy center for reading. To recognize their effort and motivate them to do their task continuously and efficiently and considering the limited resources to support their implementation, the Region has been granting monthly mobilization allowance to these Informal Laboratory Workers. With this initiative, the problem of inaccessibility of diagnosis services due to unavailability of transportation, lack of manpower, peace and order problem and geographical barriers are addressed.

OS2-2

Specific differentiation of Mycobacterium bovis from Mycobacterium tuberculosis of the Mycobacterium tuberculosis complex by molecular methods

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Thailand is a developing agricultural country in Southeast Asia. No report has been published regarding the prevalence of bovine tuberculosis among Thai patients. Research on epidemiological surveys of bovine tuberculosis in Thai patients is expected to be beneficial for academic data and policy development. At Drug Resistant Tuberculosis Fund, Siriraj Hospital, Mahidol University, Thailand, during 2004-2014, a total of 22,199 isolates from tuberculosis (TB) patients were identified to be *Mycobacterium tuberculosis* (MTB) (19,378 isolates) and *Mycobacterium tuberculosis* complex (MTBC) (2,821 isolates) by in-house multiplex PCR. Four hundred and eighty seven MTBC clinical isolates and 24 *M. bovis* isolates obtained from water buffaloes (*Bubalus bubalis*) in 2016 were retrieved. PCR-RFLP of *oxyR* and amplification of RD9 identified MTB (486/487, 99.8%), *M. bovis* BCG (1/487, 0.2%,) and *M. bovis* (24/24, 100%). The putative gene RvD1-Rv2031c, a 500 bp fragment, was present in all *M. bovis/M. bovis* BCG isolates and also in some MTB isolates. PCR-RFLP of the *oxyR* gene and amplification of RD9 region were 100% sensitive and specific for distinguishing *M. bovis* isolates from other complex members, but cannot differentiate *M. bovis* from *M. bovis* BCG. In this study, no *M. bovis* causing tuberculosis in Thai patients was identified.

OS2-3

Comparative performance of "LoopampTM MTBC Detection" kit for rapid detection of complex Mycobacterium tuberculosis: a retrospective study

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Background: Early and accurate diagnosis is important for the control and prevention of the infectious disease like tuberculosis. This study aims to evaluate the performance of Loopamp™ MTBC assay on frozen sputum samples of suspected TB patients, by comparing with Xpert MTB/RIF assay.

Methods: This study was conducted between 2013 and 2014 at the Institut Pasteur in Cambodia. The performance of Loopamp™ MTBC detection kit and Xpert MTB/RIF test for the detection of MTBC DNA were compared by use of 196 sputum specimens (81 smear and culture positive, 16 smear negative and culture positive and 99 smear and culture negative).

Results: The Loopamp™ MTBC assay and Xpert MTB/RIF were highly specific and exhibited excellent sensitivity (100%) with smear positive specimens. Both methods exhibited similar sensitivities with smear negative specimens (56.3% Loopamp MTBC and 43.8% for Xpert MTB/RIF). The overall sensitivities of the Loopamp MTBC and Xpert MTB/RIF assay were 92.8% (95% CI 85.897) and 90.7% (95% CI 83.195.7), respectively.

Conclusions: Loopamp™ MTBC assay is a simple rapid nucleic acid amplification method and well adapted to a routine TB laboratory. It appears to be as sensitive and specific as Xpert MTB/RIF assay in the detection of MTBC in sputum sample.

OS2-4

Clinical efficiency of TB-LAMP for the diagnosis of tuberculosis

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Background: Early diagnosis of tuberculosis remains difficult, particularly in resource-limited settings. We aimed to evaluate the clinical efficiency of TB-LAMP (Eiken Co., Japan) for the diagnosis of active pulmonary tuberculosis.

Methods: We performed head-to-head comparison of mycobacterial detection assays on sputum samples from 284 subjects presenting symptoms of presumed TB in the Ulaanbaatar city. Result of Ogawa was compared to smear microscopy, TB-LAMP and GeneXpert MTB/RIF for all samples.

Results: With 284 (100%) valuable tests, 197 (69.3%) were smear negative and 87 (30.6%) were smear positive. Compared to culture, sensitivity and specificity of each examination was as follows: smear examination; 70% (95% IC 60.8-77.8) and 98.2% (95% IC 94.3-99.5), GeneXpert MTB/RIF assay; 99.2% (95% IC 94.7-99.4) and 91.9% (95% IC 85.3-95.8), TB-LAMP; 91.9% (95% IC 85.3-95.8) and 96.3% (95% IC 91.6-98.4). In total, 124 (43.6%), 133 (46.8%) were MTB positive with smear examination, TB-LAMP and GeneXpert TB/RIF, respectively (p=0.499).

Conclusion: The TB-LAMP test showed high sensitivity and specificity for TB detection in TB suspects. There were no statistically significant difference observed for sensitivity and specificity between TB-LAMP and GeneXpert MTB/RIF tests.

OS2-5

Comparative Performance Study of LoopampTM MTBC Detection Kit for Rapid Detection of Mycobacterium tuberculosis Complex in Cameroon

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Background: One of the main obstacles in global tuberculosis (TB) control is the lack of highly sensitive and specific point-of-care (POC) diagnostic tests. The objective of this study was to assess the performance of Loop-mediated Isothermal Amplification (LAMP) on unprocessed sputum samples of suspected TB cases.

Methods: The study was conducted at the Yaoundé Jamot Hospital Laboratory and at the Mycobacteriology National Reference Laboratory of Centre Pasteur of Cameroon in Yaoundé. Five hundred and twenty seven consecutive patients were included in the study. Smear microscopy, LAMP test, GeneXpert® MTB/RIF and MGIT Culture were performed on sputum samples from suspected pulmonary TB patients.

Results: The LAMP test and smear microscopy showed sensitivities of 82.6% (95% CI, 76.9-87.2) and 53.6% (95% CI, 46.8-60.3) respectively and specificities of 96.0% (95% CI, 93.2-97.7) and 99.0% (95% CI, 97.1-99.7) respectively, compared to culture. The sensitivity and specificity of LAMP were slightly similar to GeneXpert®, (89.9%; 95% CI, 85.0-93.3) and (97.0%; 95% CI, 94.4-98.4) respectively.

Conclusion: The LAMP test was more sensitive than currently used microscopy. The LAMP test presents a promising diagnostic tool for TB in peripheral laboratories with limited equipment such as those in developing countries.

Keys words: Tuberculosis, LAMP test, smear microscopy, GeneXpert® MTB/RIF, MGIT culture

OS3-1

Treatment outcomes in patients with Multidrug resistant TB and other Drug Resistant TB in Cambodia: an 8-year experience

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Background:

Cambodia started to launch Multidrug-resistant tuberculosis (MDR-TB) program in 2006.

Objective and Methods:

We retrospectively analyzed the clinical records of all DR-TB patients with culture-proven MDR-TB or DR-TB or GeneXpert who were registered from 2006 to 2013 at 9 MDR-TB treatment sites of Cambodia. Poor outcomes was defined as a combination of death, failed and lost to follow-up.

Results:

A total of 474 patients were enrolled for second line TB regimen. 163 (34%) were female. HIV co-infection was presented in 104(22%). The treatment outcomes among MDR-TB/RR-TB group were (n=409): 327(82%) cured/completed; 59(15%) died; 3 failed; 2(5%) lost follow-up. Poor outcomes were significantly associated with HIV co-infection (OR: 1.7, 95% CI: 1.0-3.0, p=0.03), a BMI less than 18.5 kg/m^2 (OR: 2.0, 95%CI: 1.1-3.7, p=0.02); resistance to RHES or XDR-TB/pre XDR-TB by confirmed DST (OR: 2.5, 95%CI: 1.2-5.2, p=0.00). The risk factors for poorest outcome (death; n=59), was found significantly among HIV-infected patients (OR: 2.0, 95%CI: 1.1-3.7, p=0.01), BMI< 18.5 kg/m^2 (OR: 2.9, 95%CI: 1.3-6.4, p=0.00).

Conclusion:

The overall successful treatment outcome was achieved at least as high as in published studies. However, the presence of HIV confection, low BMI, patients who confirmed resistance to 4 first line drugs or XDR/preXDR-TB are independent prognostic factors for poor outcomes.

OS3-2

Primary Drug Resistance is the Major Cause of Resistance Among Treated Tuberculosis Patients in Shanghai, China

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It is generally believed that drug resistance among treated tuberculosis (TB) patients is as a result of treatment failure due to acquired drug resistance. In this study, we tested the hypothesis that drug resistance among treated TB patients is not only caused by acquired resistance. We used MIRU-VNTR to genotype first and second *Mycobacterium tuberculosis* isolates from treated pulmonary TB patients in Shanghai; to determine whether resistance is as a result of primary drug resistance; (i.e. resistance due to re-infection by a drug resistant strain or acquired drug resistance (i.e. resistance due to therapy failure). Among the 99 patients with increasingly drug resistance, paired isolates from 25.3% (25/99) had identical VNTR pattern in first and second isolate suggesting acquired drug resistance. Conversely, paired isolates from 74.7% (74/99) had different VNTR pattern in first and second isolate. This indicates that a greater number of the patients, 74.7% had tuberculosis due to transmitting primary drug resistance strains. Therefore, our results has demonstrated that transmission, rather than acquired resistance is the major cause of drug resistance among treated TB patients in Shanghai; thus, there is need for urgent strategies aimed at preventing and interrupting transmission to reduce the risk of drug resistant tuberculosis.

OS3-3

Multidrug-Resistant Tuberculosis in Singapore

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Introduction
Singapore, a multi-racial city-state, had 1.63 million long-stayer non-residents among a total population of 5.53 million in 2015. The city also receives large numbers of travelers, including medical tourists from high TB incidence countries.
Objective
We studied the clinical characteristics of all multi-drug resistant tuberculosis (MDR-TB) patients diagnosed in Singapore and the treatment outcomes of Singapore residents.
Methods
This was a retrospective observational study using data captured between January 2005 and December 2013 in the national tuberculosis registry. Epidemiological, microbiological, clinical and radiological features were described. Treatment outcomes of residents were evaluated.
Results
Among 207 MDR-TB cases, 155 (74.9%) were non-residents. Significantly more residents presented with cough (76.1% vs. 60%, p=0.048). A higher total number of extensively drug-resistant tuberculosis (XDR-TB) and pre-XDR-TB patients were found in non-residents vs. residents (19.4% vs. 3.8%, p=0.058). Of the 52 residents with MDR-TB, 44 (84.6%) successfully completed treatment. Mean duration of treatment was 20.4 months. Number of patients with failure of treatment, deaths and transfer out were one (1.9%), five (9.6%), and two (3.8%) respectively.
Conclusions
Non-residents constitute the majority of MDR-TB in Singapore. A high rate of treatment success among Singapore residents was achieved due to a strict public health programme.

OS3-4

pncA mutations are associated with slower sputum conversion during the WHO standard treatment of multidrug-resistant tuberculosis

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Background The value of drug resistance molecular diagnosis to guide the treatment of multidrug-resistant tuberculosis (MDR-TB) remains unclear. Here, we focused on the association of drug susceptibility phenotype and genotype with treatment outcomes in patients with MDR-TB. Methods In a prospective cohort study, we enrolled 252 consecutive patients with confirmed MDR-TB between 2010 and 2013, and outcomes were followed-up over the 24-month treatment course in terms of clinical manifestation and sputum conversion. Results Among the 252 MDR-TB isolates, 88 (34.9%) were resistant to fluoroquinolones and/or Aminoglycosides, with 65 (73.9%) containing mutation in drug resistance-related genes. Among those with known outcomes, treatment succeeded in 82.8% with plain MDR-TB, 69.7% with initial resistance to either a fluoroquinolone or Aminoglycosides, 47.5% with genetic mutation in drug resistance-related genes, 29.3% with initial XDR-TB. In multivariate analysis, pyrazinamide resistance and its related pncA gene mutation was independently associated with a lower risk of culture conversion on at 8 weeks and treatment success, while fluoroquinolone resistance was negatively correlated with treatment success. Besides, Specific treatment, patient and program variables were also associated with treatment outcome. Conclusion DST for pyrazinamide and fluoroquinolones together with genetic information appears to provide a clinically useful indicator of the treatment outcome of MDR-TB in China.

OS3-5

Body Mass Index on Six-month Sputum Culture Conversion in Multi-Drug Resistant Tuberculosis Patients

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Background:

Sputum culture conversion within 6 months intensive anti-tubercular therapy is an important predicator for treatment success in multi-drug resistant tuberculosis (MDR-TB) patients. The aim of this retrospective analysis is to highlight the BMI on sputum culture conversion.

Methods:

From May 2007 to February 2016, 177 MDR-TB patients in central and eastern Taiwan region under DOTs-plus care with individualized regimen were enrolled. The Cox proportional hazards models was conducted for hazard ratio (HR) and multivariate analysis.

Results:

The six-month sputum culture conversion rate was 74% (n=131, median: 48 days). The multivariate analysis showed Body mass Index (BMI)<18.5 kg/m^2 (HR=0.56; 95%CI=0.35-0.91), BMI≧24 kg/m^2 (HR=0.60; 95%CI=0.38-0.96) at the diagnosis of MDR-TB, cavitation on chest radiograph (HR=0.64; 95%CI=0.44-0.94), previous TB treatment (HR=0.54; 95%CI=0.37-0.79) and Fluoroquinolones (FQs) resistance (HR=0.43; 95%CI=0.25-0.74) were unfavorable factors. Conversely, use of more than 6 effective drugs in intensive phase (HR=2.21; 95%CI=1.48-3.30) [Table 1] and patients with normal BMI [Figure 1] are favorable indicators contributing to six-month sputum culture conversion.

Conclusions:

Except of containing more than 6 effective drugs in intensive phase, normal BMI is also a important factor contributing to six-month sputum culture conversion.

Key words: *Multidrug resistant tuberculosis, Sputum culture conversion, Body mass index.*

OS4-1

Documenting prevalence of childhood TB in a village community in Sindh—Policy implications for TB programs

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Background: TB prevalence among childhood population is estimated to be between 4%-21% in High Burden Countries but more granular numbers are needed to target specific interventions.

METHODS: Based on routine programmatic analysis, a hotspot for TB cases was identified in Jamshoro district. A door to door household survey was undertaken with all households of the village in December 2015. Residents were verbally screened for symptoms of TB by community health workers using android based decision support system and presumptive TB suspects were referred for evaluation and testing to a government TB centre.

RESULTS:

200 households were approached in which 726 children were screened, 189 (26%) suspected and 95 (13%) investigated for TB; 356 adults were screened, 45 (13%) suspected and 17 (5%) were investigated for TB. Of those investigated, 40 children and 6 adults were found with disease. Prevalence of TB was estimated to be 6% and 2% amongst children and adults, respectively.

CONCLUSION: The prevalence of childhood TB in a peri-urban district of Sindh is estimated to be 6%. We believe that this estimate is at the lower end as not all presumptive TB suspects came for clinical investigation. Targeted active screening intervention can increase case notification of childhood TB.

OS4-2

Enhanced pulmonary TB case detection among children at a rural chest diseases center in Pakistan

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Background:
An estimated 0.5 million children develop TB annually accounting for 6-10% of all TB cases. This is likely an underestimate of the true child TB burden, owing to poor access to diagnostics and underreporting. We report results of a focused intervention conducted at a rural chest center in Pakistan.

Methods
Lay screeners trained on android based interactive algorithms and deployed in the outpatient clinics, referred presumptive cases for a clinical and diagnostic evaluation to a medical officer. Children with TB underwent appropriate treatment based on WHO guidance.

Results
Screeners assessed 10534 children between May 2015 and March 2016, of which 3411 needed further evaluation. Of these, 675 (6.4%) children were diagnosed with TB disease and started treatment. Among those with TB, 276 (40.8%) were females, 330 (48.8%) were below 5 years of age and 645 (95.5%) had pulmonary TB. Child TB notification increased 3.07 times at project conclusion.

Conclusion
Case finding through verbal screening resulted in 3 times more children with TB, who reached effective treatment. Efforts directed at a chest center resulted in a high yield of pulmonary TB.

OS4-3

Vitamin D in TB Prevention in School Age Children in Mongolia

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Background
it is ongoing study started in 2015 and will last by 2019.
Both in vitro and animal studies provide evidence of a protective relationship between vitamin D and the risk of acquiring latent TB infection. The evidence underpinning the trial we conducting is compelling.
In this study, we aim examining the followings
Primary aim. Determine the extent to which 14000 IU of vitamin D weekly (equivalent to 2000 IU daily) reduces the risk of latent tuberculosis infection (LTBI) in children.
Secondary Aim 2. Determine whether this regimen of supplementation reduces incidence of active TB disease.
Secondary Aim 3. Determine whether any protective effect of vitamin D supplementation is dependent on baseline serum 25-hydroxyvitamin D (25[OH] D) concentration.
Methodology
It is double blinded study. Participants randomized to receive vitamin D or placebo in a 1:1 ratio.
Findings
Screening started by 01.09.2016. We screened 9137 children using IGRA and excluded 908 children with LTBI and initially recruited 8200 children aged 8-13 years from 15 schools of Ulaanbaatar. Out of 908 children 692 were further examined and we found 103 had active TB.
We also found link between LTBI passive smoking, housing, TB contact and age.
Funding-NIH funded Harvard study

OS4-4

Hospitalized Pediatric Antituberculosis Drug Induced Hepatotoxicity: Experience of an Indonesian Referral Hospital

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ABSTRACT

Introduction: Although its incidence in children is reported low, hepatotoxicity due to antituberculosis drugs is serious. Dr.Hasan Sadikin Hospital (RSHS) is a referral hospital in West Java, Indonesia.

Methods: Hospitalized pediatric ADIH medical records from October 2010 to 2015 were reviewed retrospectively through computer-based search. Correlation of characteristics and occurence of ADIH were analyzed using Pearson Chi-Square.

Results: Fifty (3.5%) out of 1424 pediatric TB developed ADIH; 20 (40%) were boys and 30 (60%) girls. More than half were <5 years old and 33 (66%) were malnourished. ADIH occured in 29 (58%) treated for Pulmonary TB, 15 (30%) for extrapulmonary TB and 6 (12%) for both; 34(68%) occured during the intensive phase. We identified hepatic comorbidities including CMV infection 1(2%), typhoid 1(2%), and use of other hepatotoxic drugs such as chemotherapy, antiepileptics, and antiretrovirals 9(18%). Correlation between gender, age, type of TB, duration of therapy and hepatic comorbidities to occurence of ADIH were statistically insignificant (P=0.26; 0.24; 0.97; 0.79; and 0.91 respectively). We treated pediatric ADIH using modified British Thoracic Society guidelines.

Conclusions: Pediatric ADIH in our hospital is quite frequent, thus pediatric guideline is mandatory. Further study is needed to identify risk factors such as genetic acetylator state.

OS4-5

IPT: Preliminary results from a rural setting in Pakistan

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Isoniazid Preventive Therapy (IPT) has been shown to prevent TB in the more vulnerable children, those exposed to TB at home. However, our Karachi program reported that only 35% children completed IPT, and most rural centers did not have IPT programs prior to our intervention.

We analyzed data from four health facilities in district Jamshoro, February 2015 to June 2016. All under 5 contacts of enrolled TB patients presenting to the clinic for evaluation and found free of TB, were offered Isoniazid at a dose of 10mg/kg once a day for 6 months and followed monthly. Families received travel reimbursement, counseling, reminder phone calls and household visits, as needed.

Over 17 months of program implementation, 120 children were started on IPT. Outcomes: 23 (19%) completed 6 months of IPT, whereas 20 were lost to follow-up. The mean age of children started on IPT was 2.7, with a male to female ratio of 0.9, however more girls 12/20 (60%) were lost to follow-up. None of the children who completed IPT developed TB during 6 months' follow-up.

Our results indicate that improved uptake and adherence rates can be achieved when an IPT program with incentives and counseling is introduced in rural centers.

OS4-6

Characteristics and Surgical Outcomes of Tuberculous Meningitis and of Tuberculous Spondylitis in Pediatric Patients at Dr. Hasan Sadikin Hospital, Bandung, Indonesia

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The manifestations of extrapulmonary tuberculosis (TB): TB meningitis (TBM) and TB spondylitis (TBS). Children diagnosed TBM from 2009-2014; TBS from 2004-2014 were recruited. There were 123 children with TBM (53) and TBS (70); The youngest age of TBM was 2 months old, the oldest was 14 years old (yo) median 5 yo. By modified British Medical Research Council divided as Stage I (3 cases), Stage IIa (3 cases), Stage IIb (23 cases), Stage III (24 cases). All TBM children developed hydrocephalus, with 36 cases performed ventriculoperitoneal shunt and 17 cases external ventricular drainage. In TBM children, 9.4% (5/53) had vegetative state and mortality rate was 20.8% (11/53). Hospital discharge result for TBM correlated with Glasgow coma scale pre operation (p<0.001). In TBS, the youngest age was 6 months old, the oldest was 14 yo, median 7 yo. The thoracic spine was involved in 67.1% cases, lumbar in 28.6% and cervical in 4.3%; 45 patients with neurological deficit and 25 patients without one. Of 24 children underwent spine surgery; 6 patients had anterior decompression spinal fusion and 18 patients had posterior debridement with stabilization. In TBS patients, mortality rate was 1,4% (1/70). The surgical outcomes of TBM and TBS remains poor.

OS5-1

Significance of Xpert® MTB/RIF for the detection of Mycobacterium Tuberculosis and Rifampicin resistant TB in Resource limited setting of Enugu State, Nigeria

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Background: Tuberculosis is a major public health problem in Nigeria. The World Health Organization estimates the annual TB Incidence to be 323 per 100,000 population of which 2.9% are Multi-drug resistant (MDR) TB cases. Objectives of the study were to determine MTB Positive/RIF Resistance cases among presumptive TB cases to help in public health planning and evaluate the significance of Xpert® MTB/RIF in Resource limited setting.

Design/Methods: Study was carried out in Enugu State, South East Nigeria. Data were retrospectively collected from the 3 Xpert laboratories between January 2014 and December 2015. The National GeneXpert/MTB/RIF Quarterly report form was the tool used to report and collect data. Data was analyzed with Microsoft excel.

Results: Between January 2014 and December 2015, 1,653 (51.4% males and 48.6% females) presumptive TB patients were tested by Xpert on sputum. Among the 1,653 presumptive TB cases, 286 (17.3%) were positive for MTB and among these, 22 (7.7%) were Rif resistant.

Conclusions: This study has shown the significance of Xpert® MTB/RIF in the detection of MDR-TB cases thereby decreasing the incidence of MDR-TB by identifying the patients with MTB positive/RIF Resistance. All the 22 (7.7%) MTB/RIF Resistant cases identified in this study were referred to an MDR-TB treatment center and treated as presumptive MDR cases.

OS5-2

Comparison of two drug susceptibility testing methods of fluoroquinolones for cross resistance analysis in vitro

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Objective Aim to compare two drug susceptibility testing (DST) methods of fluoroquinolones for cross resistantce analysis in vitro. Methods MGIT 960 system was used to DST with reference concentrations (2μg/mlofloxacin (Ofx), 2μg/ml levofloxacin(Lfx) and 0.25μg/mlmoxifloxacin(Mfx), respectively). The MIC values of Ofx, Lfx and Mfx were tested in 96-well plate. ResultsAccording to results of MGIT 960, 48.8%(21/43) and 97.7%(42/43) of strains resistant to Ofx were resistant to Lfx and Mfx respectively. 100%(21/21) of strains resistant to Lfx were also resistant to Mfx. MIC values of Ofx were significantly higher than those of Lfx(t=7.639, $p<0.0001$) and Lfx MIC values of 97.7%(42/43) of strains less than Ofx MIC values. MIC values of Lfxwere significantly higher than those of Mfx(t=8.196, $p<0.0001$) and Mox MIC values of 88.4%(38/43) of strains were less than 1/4 fold of Lfx MIC values. Conclusions DST of MGIT 960 suggested high rates of the cross-resistance between any two drugs of Ofx, Lfx and Mfx, especially between Ofx and Mfx. But MIC values showed the bactericidal activity of Mfx was significantly higher than that of either Ofx or Lfx. So analysis method of cross resistance of fluoroquinolonesshould be further study according to clinical therapy effects.

OS5-3

Evaluation of the new improved version of GenoType MTBDRsl line probe assay to detect extensively drug-resistant tuberculosis (XDR-TB), a multi-center study in China

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Objective: Rapid and reliable detection of resistance to second-line injectable drugs and fluoroquinolones is vital for adequate multidrug-resistant tuberculosis (MDR-TB) patient management. This study aims to assess diagnostic performance of the 2nd-generation of GenoType MTBDRsl for rapid detection of mutations conferring resistance to these drugs, and to determine the impact on the turnaround time in a multi-center study.

Methods: Totally 98 specimens from the same number of consecutive MDR-TB patients were tested in the four study sites. The diagnostic performance was assessed relative to the reference phenotypic drug-susceptibility testing method.

Results: Of 98 patient specimens, 93 had valid results. The sensitivity for detecting resistance to fluoroquinolones, aminoglycosides, and their combination (XDR-TB) was 78.3%, 88% and 86.3%, respectively; and the specificity was 98.1%, 99.4%, and 99.6% respectively. Implementation of this test significantly reduced the average turnaround time between sample receipt and result reporting from 58 to 6 days (p<0.001).

Conclusions: With a short turnaround time, the GenoType MTBDRsl assay may be a useful tool for making early decisions in patients with severe drug resistance including XDR-TB. This is important both for public health aspects (reduced transmission of resistant TB strains) and for the individual patient.

OS5-4

Detection of drug resistance isolates from false-negative vials of MGIT-960 instrument

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Background: The live bacteria of mycobacterial species can sometimes be often assumed as culture negative by Mycobacterium Growth Indicator Tube (MGIT), when it forms macrocolonies (granules). Observation of instrument negatives culture tubes for cord formation has never been studied.

Methods: Seventy-one instrument-negative liquid culture tube, was re-evaluated for the presence of granule formation followed by ZN-staining, immunochromatographicc assay (ICA) by doing subculture on liquid media. Drug susceptibility test (DST) was performed for first-line and second-line drugs on the recovered culture isolates.

Results: Thirty-one lymph node aspirate and forty smear negative sputum specimens; culture vials (MGIT tube) were found to be cords and ICA positive, respectively. In total, 71 tubes, 6.4% (2/31) was MDR-TB from EPTB specimens and 15% (6/40) were MDR-TB from sputum smear negative specimens. The emergence of fluroquinolones mono-resistance was 4.2% (3/71) observed.

Conclusions: The tiny flakes of *Mtb* (granules) present in negative fagged tubes by MGIT-960, are needed to keep an eye on these culture tubes as they consisted of very low bacillary amount. The need of visual inspection and cord formation followed by ICA testing is mandatory to increase the recovery rate of *Mtb* among sputum smear negative and EPTB cases.

OS6-1

Active case-finding for tuberculosis by mobile teams in Myanmar: yield and treatment outcomes

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Background: Since 2005, the Myanmar National Tuberculosis Programme (NTP) has been implementing active case finding (ACF) involving mobile teams. This study revealed the contribution of mobile team activities to total tuberculosis (TB) case detection, characteristics and treatment outcomes of TB patients detected by mobile teams.

Methods: This study was a descriptive study using routine programme data (October 2014-December 2014). The algorithm of case detection included screening patients by symptoms, then by CXR followed by sputum microscopy for confirmation. Diagnosed patients were started on treatment and followed until a final outcome was ascertained.

Results: A total of 9349 people with symptoms suggestive of TB were screened by CXR, with an uptake of 96.6%. Of those who were meant to undergo sputum microscopy, 51.6% had sputum examinations. Finally, 504 TB patients were identified and the overall contribution to total case detection in the respective townships was 25.3%. Treatment success rate (TSR) was high as 91.8% in study townships.

Conclusion: This study confirmed the feasibility, acceptability and effectiveness of ACF by mobile teams, using portable, digital CXR machines. However, the follow-up sputum examination created a significant barrier for confirmation. In order to optimize the mobile team activity, future activities were needed to be strengthened one stop service including molecular diagnostics.

OS6-2

Withdrawn

OS6-3

The acceptability of chemical prophylaxis for latent tuberculosis infection among student contacts of tuberculosis in Shanghai, China

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Background: Chemical prophylaxis for latent tuberculosis infection (LTBI) can reduce the risk of tuberculosis (TB) reactivation. Students are susceptible to LTBI from contact due to clustering activities. This study aimed to understand the acceptability of prophylaxis for LTBI among student contacts of TB in Shanghai.

Methods: Ten high school/college students were diagnosed of TB in three districts of Shanghai during 201605-201606. TB-screening including Chest-X-Ray was provided to the contacts of patients in schools. Questionnaire interviews were given to understand their knowledge on TB and the accessibility of prophylaxis for LTBI.

Results: Totally 425 student contacts participated in the investigation. The average age was 17.9 years and boy students accounted for 73.6%. Extent of contact was ranked into 4 groups from high to low with 12.7% being the closest contacts. Only 15.8% of the 425 students knew the core knowledge of TB. About 84.0% of the participants were willing to take prophylaxis if they had contacted TB patients. Multivariate analysis showed that extent of contact (OR=7.27) and TB knowledge sores (OR=4.69) were associated with the intention to prophylaxis.

Conclusion: Chemical prophylaxis for student TB contacts should target at the close contacts. TB health education helps to improve the acceptability of prophylaxis.

OS6-4

Finding of the first national TB prevalence survey in Mongolia, 2014-2015

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Background: Tuberculosis (TB) is a major public health concern in Mongolia. The World Health Organization (WHO)-estimated prevalence rate of all form TB was 254 per 100,000 populations in 2013. In order to obtain a reliable estimate of TB prevalence in the country to justify an improved national TB control strategy, a national population-based survey was carried out in 2014-2015.

Methods: A population based, cross-sectional survey was conducted using stratified cluster sampling. The survey was carried out in two phases: Phase 1 in urban stratum in the first year, and Phase 2 in rural and remote strata in the second year.

Results: Of 60,031 eligible subjects, 50,309 participated in the national population-based survey. A total of 88 smear-positive cases and 160 smear-negative, culture-positive TB cases were identified. The weighted prevalence rates of smear-positive and bacteriologically-positive tuberculosis were 204 (95% CI: 143-265) and 560 (95% CI: 455-665) per 100,000 populations, respectively. Tuberculosis prevalence was higher in men than women and increased with age.

Conclusions: The prevalence rate was much higher than the WHO estimation based on routine surveillance data. The survey raised challenges for strengthening TB control in Mongolia by focusing on cases without symptoms and the elderly population.

OS6-5

The Utility of Chest Radiology from the National Tuberculosis Prevalence Survey in Mongolia, Phase 1

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Background: The National Tuberculosis (TB) Programme in Mongolia conducted the first national TB prevalence survey. This survey consisted of phase 1, the urban survey in 2014, and phase 2, the rural survey in 2015. We evaluated the significance of chest radiography (CXR), one of the screening method, to be applicable for further active case finding.

Methods: All consenting participants with a positive screen on either a symptom questionnaire and/or chest radiography (CXR) submitted sputum for smear and culture. We analyzed the radiological results of phase 1 with bacteriologically results as the reference standard.

Results: Of 27112 eligible participants from 51 clusters, 5592 participants provided at least one specimen. There were 142 bacteriologically confirmed pulmonary TB cases. CXR alone identified 135 (95.1%) cases with a corresponding sensitivity, specifi city and positive predictive value of 97.1%, 84.2% and 3%, respectively. Symptomatic cases had more cavity and greater extent of shadow compared with asymptomatic cases (p<0.0001, p 0.008).

Conclusion: CXR screening had high sensitivity, and combined symptom/CXR screening has an important role for TB suspect identification.

OS7-1

DETERMINANTS OF CLIENTS' ADHERENCE TO PUBLIC—PRIVATE MIX DOTS (PPMD) TREATMENT

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This study determined the predictors of clients' adherence to PPMD treatment. Grounded on Pender's Health Promotion Model, the study employed a descriptive correlational research. Anti-Tuberculosis Chemotherapy Adherence Index derived the data and was processed using Statistical Package for Social Sciences (SPSS) version 16. A discriminant analysis was conducted to predict adherence with age, educational attainment, income, sputum smear status, accessibility, co-morbidity, perceived self-efficacy, quality of health services, perceived social support, perceived social stigma, motivation, side-effects and adverse reactions to treatment as the variables. Significant mean differences were observed among quality of health services (p= 0.007), income (p=0.030) and perceived social stigma (p=0.032). The discriminate function revealed a significant association between groups and all predictors, accounting for 71.4% of between group variability, although closer analysis of the structure matrix revealed only three significant predictors, namely quality of health services (0.476) directly influences while income (-0.381) and perceived social stigma (-0.376) both inversely influence adherence. Clients' adherence towards Public-Private Mix DOTS (PPMD) treatment is an interplay of the health care delivery system and socioeconomic factors. Hence, National TB program managers need to develop an evaluation tool for provision of health services; frequent counseling and assistance be provided pro-actively.

OS7-2

Trend of Tuberculosis incidence since 1987, Chiang Rai, Thailand: Impact of HIV epidemic and medico-social determinants

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BACKGROUND: In order to develop TB control strategies, especially in relation to HIV epidemic, we have set up the population-based field in Chiang Rai province, Thailand. Objective of this presentation is to analyze the tread of TB incidence to investigate the impact of HIV epidemic and DM as example of other medico-social determinants.

METHODS: Population-based TB registry database was computerized since 1987 in Chiang Rai province with the participation of all hospital treating tuberculosis. District-based DM registry cohort was analyzed TB incidence.

RESULTS: Annual TB incidence case reported was 707 in average 1987-1989 before HIV epidemic. Since HIV-positive TB cases was increased since firstly reported in 1990 to 880 in 1998, total number of TB cases were increased 1,931 in 1998. Even HIV-positive TB cases were decreased since 1999 until 270 in 2014, total number of TB cases was 1,556 (160 per 100,000 population as rate) in 2014. DM registry has 4,177 cases with 13,663 person years of observation and 32 TB incidence cases after DM diagnosed, therefore TB incidence rate was estimated 208 per 100,000 population. DISCUSSION: HIV epidemic has largest impact on TB incidence. The other medical/social determinants such as DM which may cause higher TB incidence need to be controlled to reduce TB incidence after HIV epidemic. Integrated care for DM and TB is necessary.

OS7-3

TRUNCATE-TB: design and implementation of a strategic clinical trial in Asia

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Two-thirds of the global TB burden is estimated to be in Asia. TRUNCATE-TB (two-month regimens using novel combinations to augment treatment effectiveness for drug-sensitive tuberculosis (DS-TB)) is a randomised, open-label, multi-arm, multi-stage (MAMS), parallel group strategy trial. The trial will be implemented at clinical sites in Philippines, Thailand, Indonesia and Singapore, with the goal of building clinical trial capacity and collaboration regionally.

The primary aim of the trial is to determine whether a strategy of treating pulmonary DS-TB for 2 months with one of a number of novel combination regimens and re-treating relapse with a 6 month course of standard treatment will be non-inferior to the WHO-standard 6 month treatment/8-month re-treatment approach in terms of TB sputum culture status at 2 years after randomisation. Secondary aims are to determine whether there are advantages of the TRUNCATE-management strategy from the patient perspective (e.g. quality of life) and programme perspective (e.g. adherence, drug resistance).

Adult patients will be randomised to receive 6 months' standard treatment as a control, or to one of a number of boosted 2-month regimens chosen for their enhanced sterilising activity (combinations of standard drugs with new or re-purposed drugs: high-dose rifampicin, linezolid, clofazimine, bedaquiline, rifapentine, or levofloxacin).

OS7-4

Assessing the impact of contact tracing coupled with preventive therapy of tuberculosis in Taiwan: an empirical individual-based modelling study

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In 2015 Taiwan Centers for Disease Control extended the ongoing TB control program of directly observed therapy and contact tracing by expanding the diagnosis and treatment of latent TB infection to all close contacts of notified TB cases, with the goal to accelerate the decline of TB incidence. Although treatment of latent TB infection among close contacts has been recommended by WHO recently, the impact of this intervention to TB epidemiology has not been extensively investigated.

We modelled TB dynamics in Taiwan by an individual-based simulation model with demographic features and contact profile in Taiwan. The parameterization was based on literature review and public surveys; the parameters were calibrated by Bayesian fitting. The main outcome measurement was the incremental reduction of cumulative TB incidence over 20 years.

The calibrated model showed that the proportion of recent latent infection among the nearest ten close contacts with any latent infection of active cases was 61.1%. Compared with no extended contact tracing, the scenario of extended contact tracing would accelerate the reduction of cumulative incidence by 29.3% (-30.0%, 91.5%) by 2035.

The simulation study suggested substantial potential impact of extended contact tracing on incidence decline. However, the uncertainty of the impact is high and warrants further clarification.

OS7-5

Medical expenditure and financial burden for pulmonary tuberculosis patients under a 'free tuberculosis treatment policy': a case study from Shanghai, China

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Background:

As the package of the 'free tuberculosis (TB) treatment policy' has been extended in Shanghai, not only first-line and second-line anti-TB drugs but also some liver-protection drugs and examinations for all pulmonary tuberculosis (PTB) patients were coved by TB control project.

Objectives:

To analyze direct medical expenditure and financial burden for pulmonary TB patients in Shanghai.

Methods:

We collected all invoices of medical expenditure for 766 PTB patients who registered and completed treatment during 2013-2015 in four districts of Shanghai.

Results:

Median (quartile) of direct medical expenditure for outpatient care was 4605.3 (3490.8, 6335.2) RMB per person for completing whole course of treatment. Drug expense accounted for 67.4%, examinations for 30.2%. Among drug expenses, liver-protection drugs accounted for more than 50% and first-line anti-TB drugs for 20%. There were 38% of all direct medical expenditure was paid by medical insurance, 23% by the 'free TB treatment policy' and 39% by out-of-pocket.

Conclusions:

The direct medical expenditure for PTB patients in Shanghai was relatively high, and especially the use of liver-protection drugs should be normalized. The 'free TB treatment policy' reduced some financial burden but the proportion of out-of-pocket was still higher for PTB patients.

OS8-1

J-shaped association between alcohol drinking and incidence of active tuberculosis in a prospective cohort of middle-aged and elderly adults

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Meta-analysis has shown that $\geq$40 g/day of alcohol intake increased risk of active TB, but effect of lower intake is unclear. Cigarette smoking, a strong risk factor of TB, is often correlated with alcohol drinking and could potentially confound the relationship. We investigated alcohol and smoking in relation to TB incidence in the Singapore Chinese Health Study, a prospective cohort of 63,257 Chinese aged 45-74 years enrolled during 1993-1998. Information on alcohol intake and smoking history was collected at recruitment. By December 2014, 1249 cohort participants developed active TB. After adjusting for smoking, we observed a J-shaped association between alcohol and TB risk (P-trend$_{quadratic}$<0.001). Compared to non-drinkers, less than daily drinkers (mean ethanol intake 32 g/week) had significant reduced risk of active TB [hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.71-0.97) while drinkers with $\geq$20 g/day of ethanol had significant increased risk (HR 1.37, 95% CI 1.05-1.79). When stratified by smoking status, reduced TB risk in infrequent drinkers was observed among non-current smokers only, while increased risk with higher alcohol intake was observed among current smokers only. Light alcohol drinking may protect against development of active TB among non-current smokers, while heavy drinking increases TB risk among current smokers.

OS8-2

A matched case-control study to identify risk determinants of tuberculosis in Bangladesh

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Tuberculosis remains a major public health problem in Bangladesh. The present study focused on identifying TB risk determinants in Bangladesh as part of national TB control programmes. An age-sex matched case-control study was conducted with each stratum consisting of one case and two controls; 360 cases and 720 controls were selected for the study. The study was conducted in six divisions covering both the rural and urban areas of Bangladesh. Information were collected via face-to-face interviews. Conditional logistic regression model was used to identify important risk factors for TB. The results showed that having secondary or higher level of education reduced TB risk by 50%, 95% CI: 0.32-0.78. Other risk factors were living in building (aOR 2.54, 95% CI: 1.43-0.4.52) compared to living in improper house/semi-building, previous history of TB (aOR 2.04, 95% CI: 1.05-3.95), smoking cigarette in the past (aOR 5.27, 95% CI: 2.82-9.86) compared to non-smokers. The findings can be used to strengthen national TB control programmes by developing social protection interventions and raising awareness about health hazard caused by smoking cigarette. Further research can be done to determine if lifestyle factors such as area of residence, malnutrition, and unhygienic surroundings have any significant effect on TB.

OS8-3

NAT2 rapid acetylator showed significant association with mortality in HIV positive tuberculosis patients

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Introduction Rapid acetylators of *N-acetyl transferase 2* (*NAT2*) was associated with tuberculosis (TB) treatment failure. However, association between *NAT2* acetylator status and death of the patients has never been reported in any population. We aimed to study the association of *NAT2* acetylators with death.

Method Subjects provided informed consent and were recruited from Chiang Rai province, Thailand. Genetically matched 165 HIV positive and 737 HIV negative TB patients with accessible mortality data were collected, and were subjected to obtain genome-wide single nucleotide polymorphisms information. *NAT2* acetylator was imputed using "impute2" and "fastPHASE". Association test was performed comparing the distributions of *NAT2* acetylator status and "death within 18 months after treatment initiation", and further stratified by HIV status.

Results *NAT2* rapid acetylator was associated with the death in HIV positive patients compared with *NAT2* intermediate acetylator (hazard odds ratio (OR): 3.55 95% confidence interval (95%CI): 1.30-10.03, P = 0.00845). Further, *NAT2* slow acetylator compared with *NAT2* intermediate acetylator did not show significant association in HIV positive patients but show similar tendency (OR: 2.30 95%CI: 0.92-6.01, P = 0.059).

Discussion The increased risk of death seen in *NAT2* rapid and slow acetylators of TB/HIV co-infection population suggested the importance of optimum drug dosage.

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Depicting recent transmissions of multi-drug resistant tuberculosis in Shanghai, China: a population-based genotypic and spatial study

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Background

China has the second largest burden of multi-drug resistant tuberculosis (MDR-TB) in the world. TB transmission is complex in large cities where internal migrants account for nearly half of cases.

Methods

A population-based genotypic and spatial analysis was conducted in Shanghai, China, January 2009 and 31 December 2012. All pulmonary cases received microscopy and culture, while positive cultures were tested for drug susceptibility. MDR-TB cases were genotyped with 12-loci variable number tandem repeats (VNTR). We estimated relative transmission rates by smear results, household status and location, and conducted spatial analyses based on patient residential addresses using kernel density estimation, K-function and D-function.

Results

367 (4.6%) MDR-TB patients were identified from 7,982 culture positive cases, while 299 (81.5%) had both genotyping and geocoding information. Of which, 110 (36.8%) MDR patients were genotypic clustered based on VNTR. The relative transmission rate for local patients versus migrants was 3.36 (95%CI 1.86-6.09, P<0.001). MDR-TB transmissions were concentrated in central urban districts. Genotype clustering patients aggregated spatially compared with non-clustered patients. Local cases (aOR 4.11, 95%CI, 2.15-8.09, P<0.001) and spatial aggregation in 3 kilometers (aOR, 4.47, 95% CI, 1.19-17.60, P=0.029) were significantly associated with genotype clustering.

Conclusions: Local patients contributed more to MDR-TB recent transmissions. MDR-TB transmissions were concentrated in central urban districts, and localized within 3km.