

Impact of Ambient Air Pollution on the Incidence of Pulmonary TB in Malaysia

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Background

- Air pollution is a leading cause of death and disability in the world and it has caused 10 million deaths per year.
- WHO reported, 92% of the world population living in places where air quality standards were not met.
- IARC: Ambient air pollution classified carcinogenic to humans and particulate matter has strong risk factor to lung cancer incidence.
- Affects the airways and altered host defense:
 - Mucociliary clearance and macrophage functions that impairs immune response to respiratory tract infections;
 - Might accelerate proliferation of *M. tuberculosis*.
- Several studies reported exposure to particulate matter and Sulfur Dioxide increased the risk of TB disease.

Air pollution & Health



CVD



Asthma



Stroke



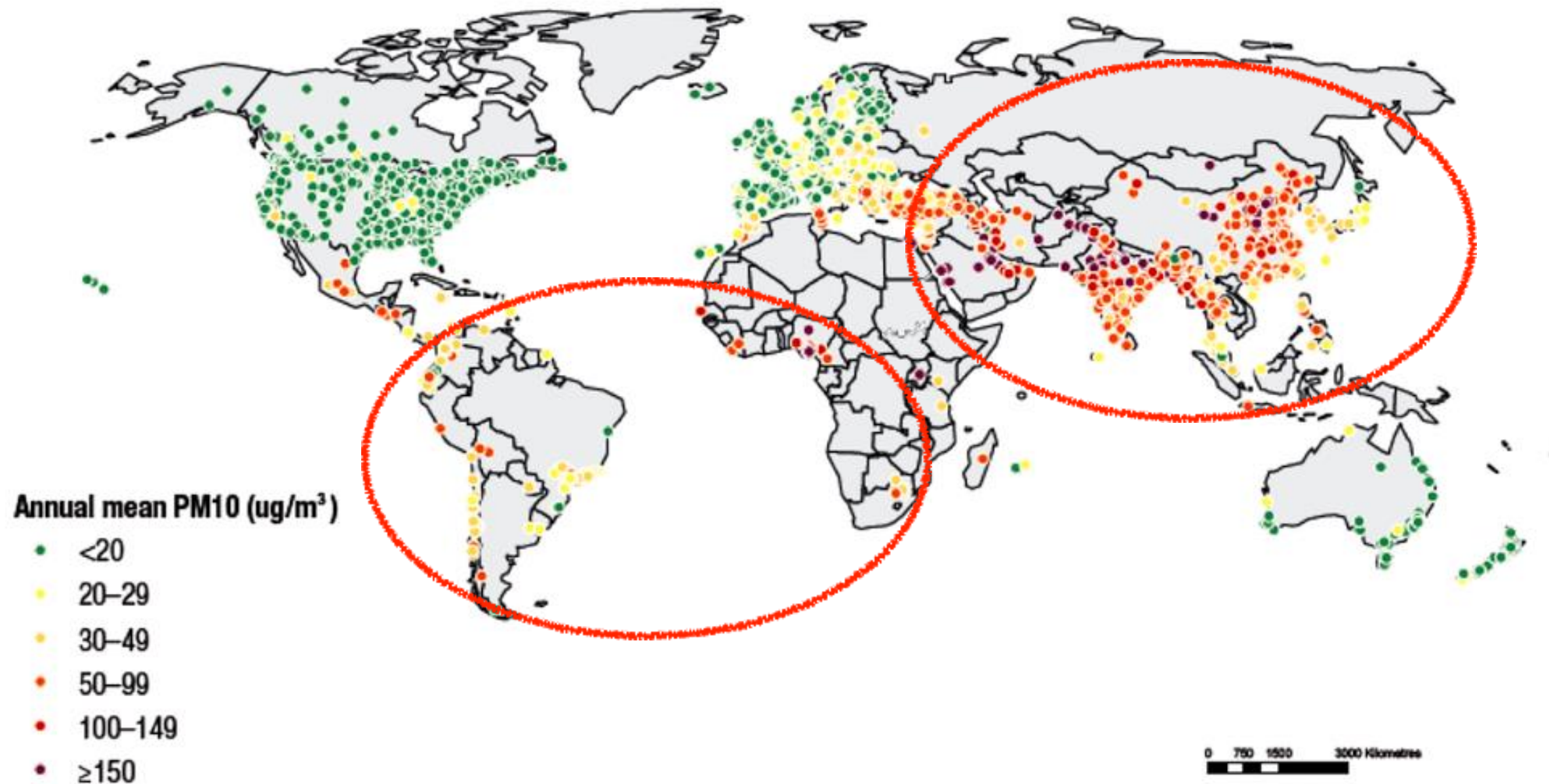
Reproductive Health
~ low birth weight



Lung Cancer

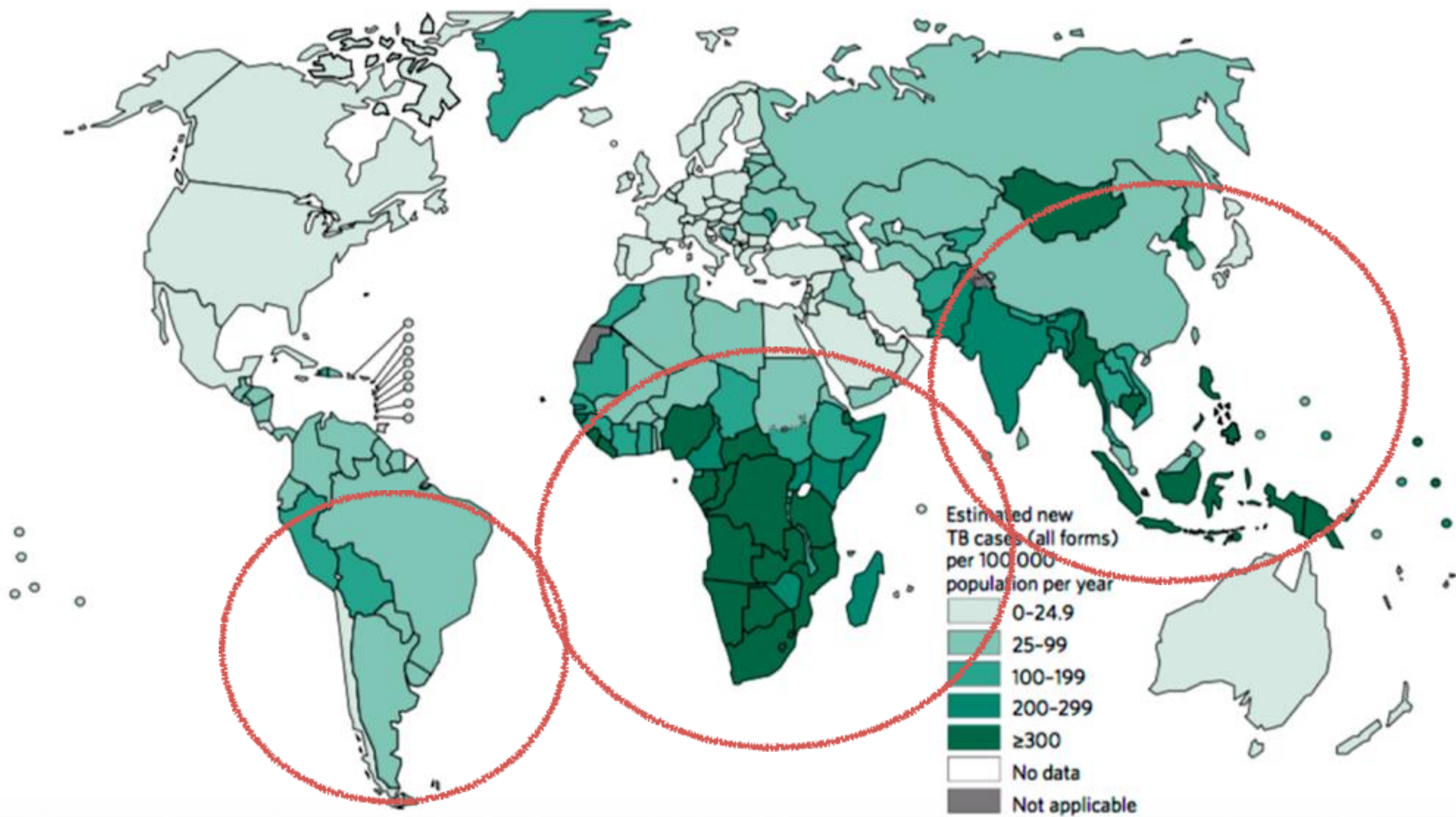
Air Pollution and Infectious Disease?

So what's the
problem?.....

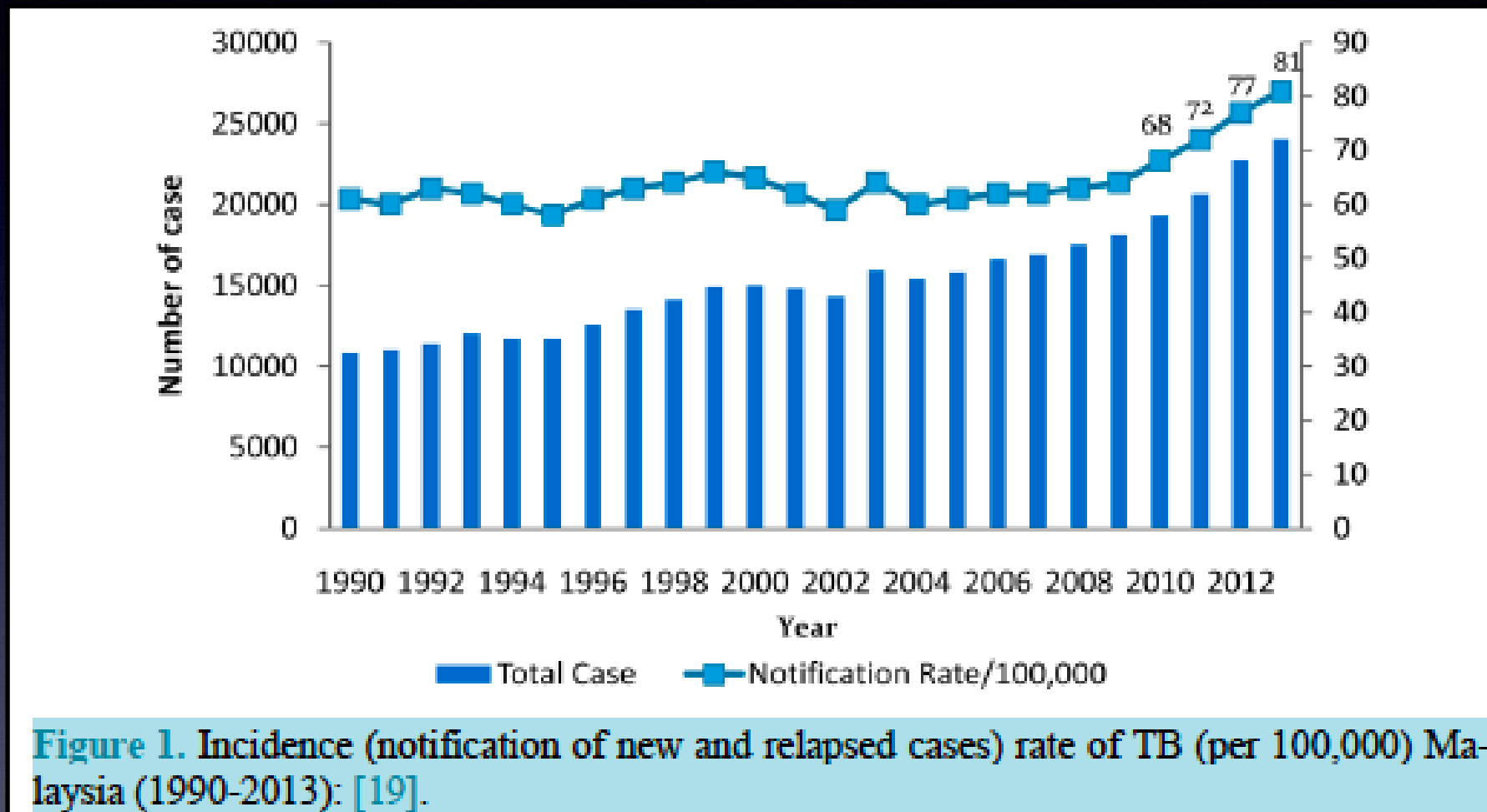


* The mean annual concentration of fine suspended particles of less than 10 microns in diameter is a common measure of air pollution.

- People in urban and developing countries exposed to high concentrations of ambient air pollution.
- Those areas also reported to have high incidences of TB.



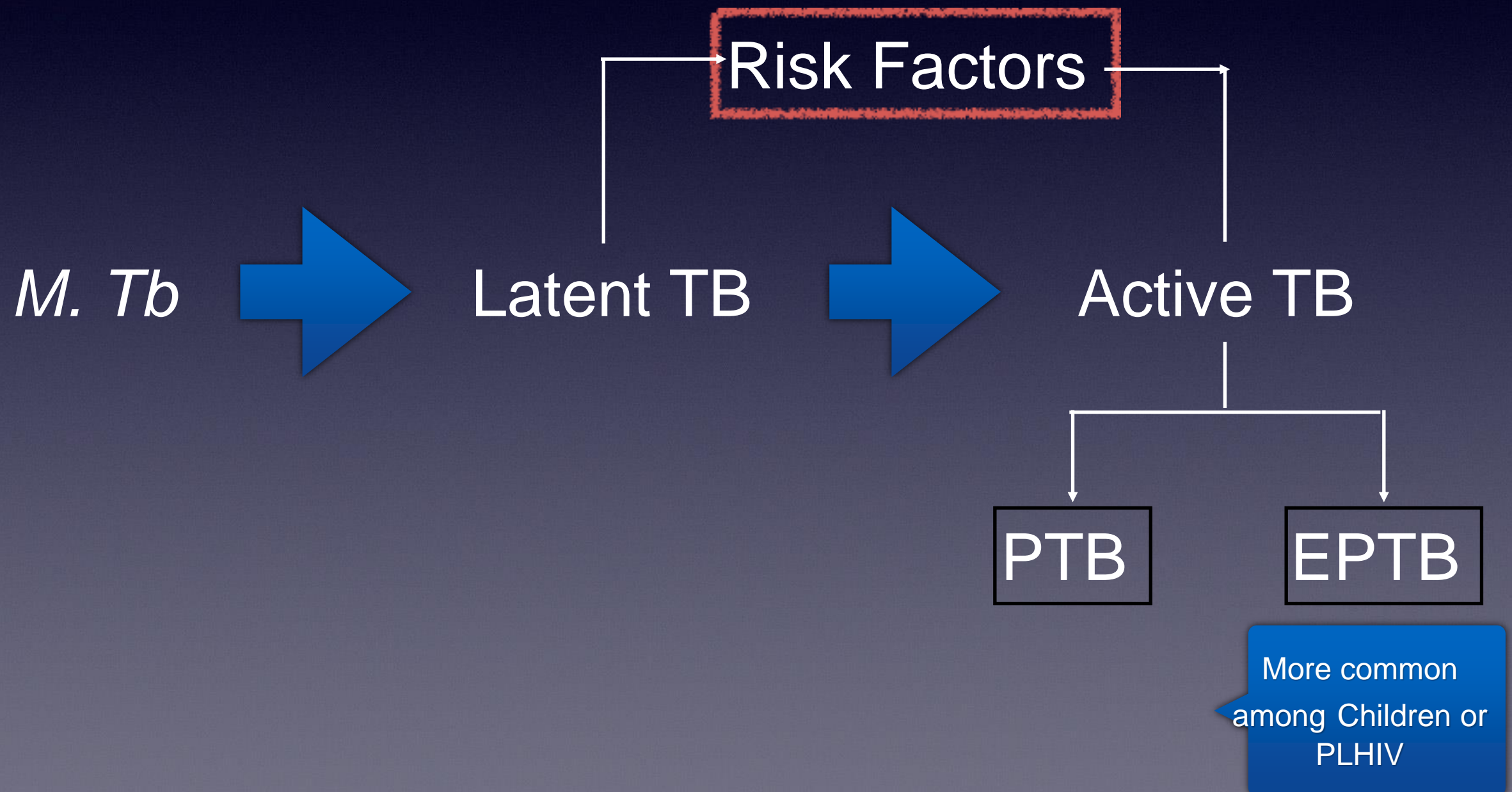
Issues: TB in Malaysia



Shajahan et.al, 2016

- Incidence of TB in Malaysia has been on rise over the years with annual TB IR=89 cases/100,000 population in 2015.
- States with high density population, urban areas were reported with higher burden of TB cases.

Risk Factors - Active TB



Risk Factors - Active TB



1. SES: Crowding, Income
2. Lifestyle: Undernutrition, Tobacco Use
3. Immunity; PLHIV, Children
4. Co-morbidities: Diabetes, Obesity
5. Environment: Indoor Air

How about
ambient air?

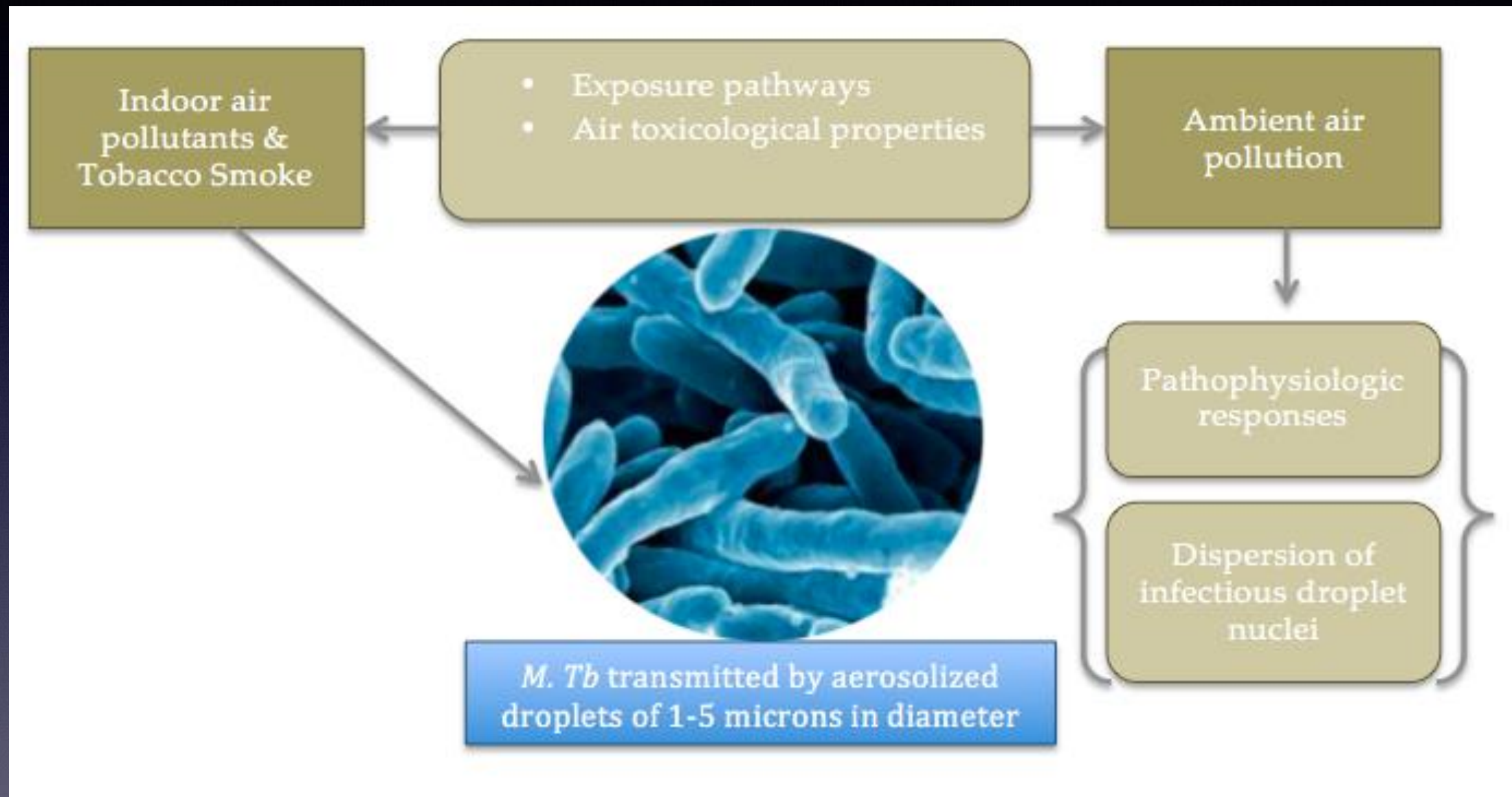
How about air
pollutants?

Could air pollutants
activate TB disease?

Findings from other studies?

- Limited study - AP and TB disease.
- Cohort study (China) - PM 2.5
- Retrospective cohort (South Korea) - SO₂
- Long term exposure of PM 2.5 - TB mortality.
- South East Asia? Not yet!

Motivation for the analysis



Impact of air pollution and the development of TB disease prior infection remain obscure.

Objective(s)

To investigate the potential role of ambient air pollution that might aggravate PTB in relative to EPTB.

Specific objectives:

1. To describe the characteristics of PTB patients in Malaysia;
2. To examine ambient air pollution exposures in each state in Malaysia;
3. To examine air pollutant exposures and their association with PTB incidence in relative to EPTB.

Methods

Study Design:

Ecological Cross-sectional; utilized a cohort of TB patients in 2013.

Population data:

We obtained data on the Malaysian population stratified by state, sex and ethnicity. We calculated standardized incidence rates of TB, PTB and EPTB for all states.

Methods

TB Cases (Outcome variable):

1. Data; National surveillance of TB information system database (TBIS) that include information on patient's socio-demography profiles, clinical diagnoses & co-morbidities.
2. Binary dichotomous outcome variable coded 1=PTB and 0=EPTB.
3. Inclusion criteria: All confirmed TB cases based on clinical AND bacteriological or radiological.
4. Exclusion criteria: TB cases confirmed MDR-TB, TBHIV, and those without HIV confirmatory status.

Methods

Air Pollution (Exposure variable):

1. 2-year exposure data from Jan 1, 2011 to Dec 31, 2013 included Air Pollutant Index (API) and 5 ambient air pollutants:
 - Sulfur Dioxide (SO₂), Nitrogen Dioxide (NO₂), Carbon Monoxide (CO), Ozone (O₃) and Particulate Matter less than 10 μ m in aerodynamic diameter (PM₁₀).
2. All transformed in μ g/m³ unit.
3. 52 air monitoring stations all over Malaysia
4. Calculated 2-year mean and 95th-per pollutants.
5. Each of TB patient was assigned with the address located to the nearest air monitor

Why 95-percentile?

- Exposure period and dose-response relationship is crucial.
- Cut-off of 95-percentile of all ambient air pollutants that might potentially drive TB disease.

Data analysis

1. Descriptive and Bivariate analysis to describe the characteristics of TB and air pollution.
2. Correlation analysis: To examine the correlation of the 2-year 95th-percentile of air pollutant variables:
 - Preliminary analysis by visual assessment of scatterplots;
 - To examine relationships of the 2-year 95th-percentile for each of the air pollutants with each other including API.
 - Pearson correlation coefficient, r to assess those relationships that significant at $p\text{-value} < 0.05$.

Data analysis

1. Logistic regression analysis: To estimate association between 2-year 95th-percentile of API and PTB in relative to EPTB by controlling covariates.
 - Preliminary crude bivariate analysis.
 - Significant predictors included in final model.
2. To control multicollinearity, separate logistic regression was done to assess the impact of five(5) air pollutants and PTB adjusted for covariates.
3. Selection of final model based on goodness of fit assessment; Hosmer & Lemoshow Goodness of fit test $p > 0.25$.
4. Also considered for the lowest AIC and BIC for each of the model.
5. Each final model included all associated exposure predictors with PTB, significant at $p\text{-value} < 0.05$.

Results

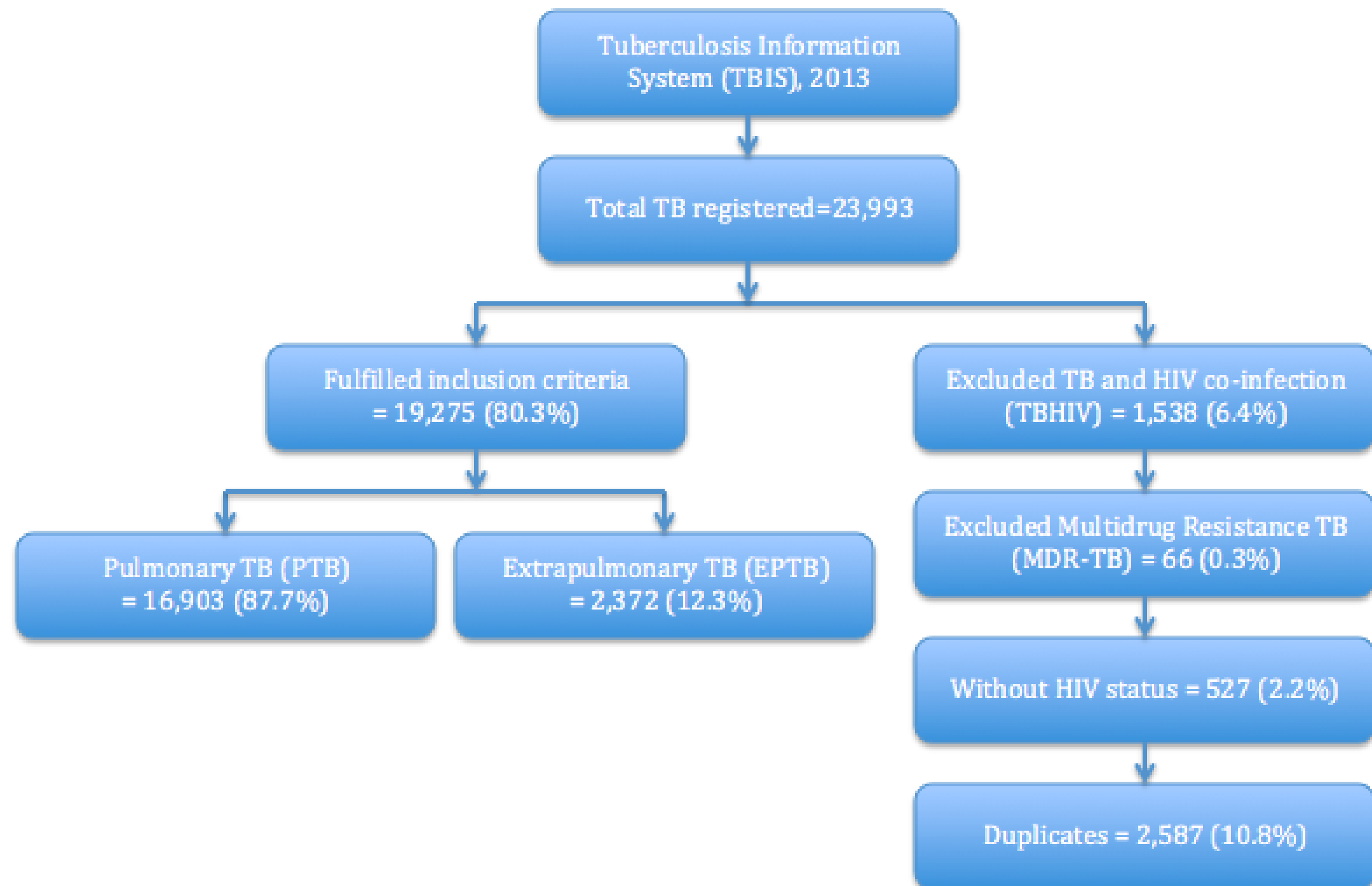


Figure 3: Sample population

Results

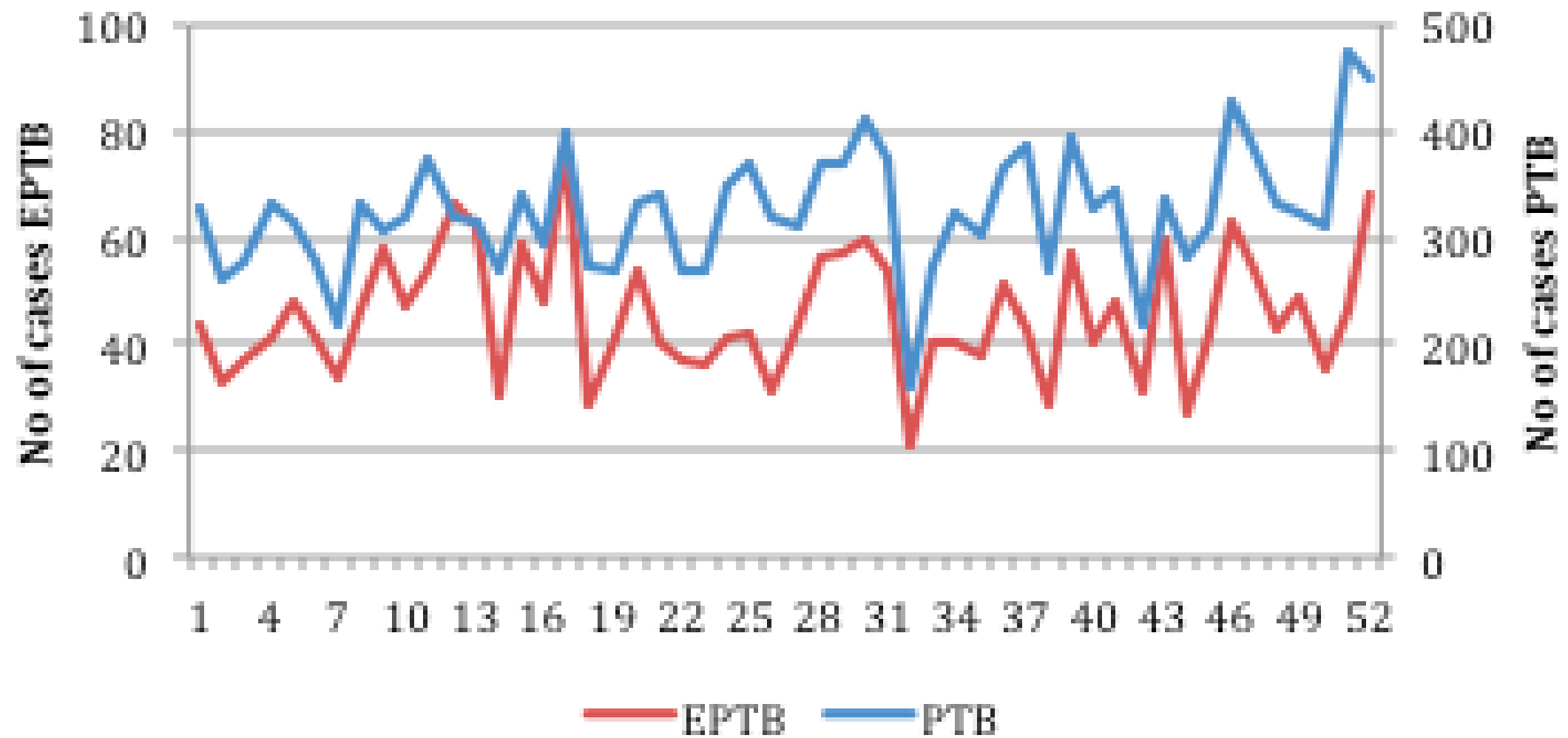


Figure 4: Notified PTB and EPTB cases by Epi-week in 2013

Results

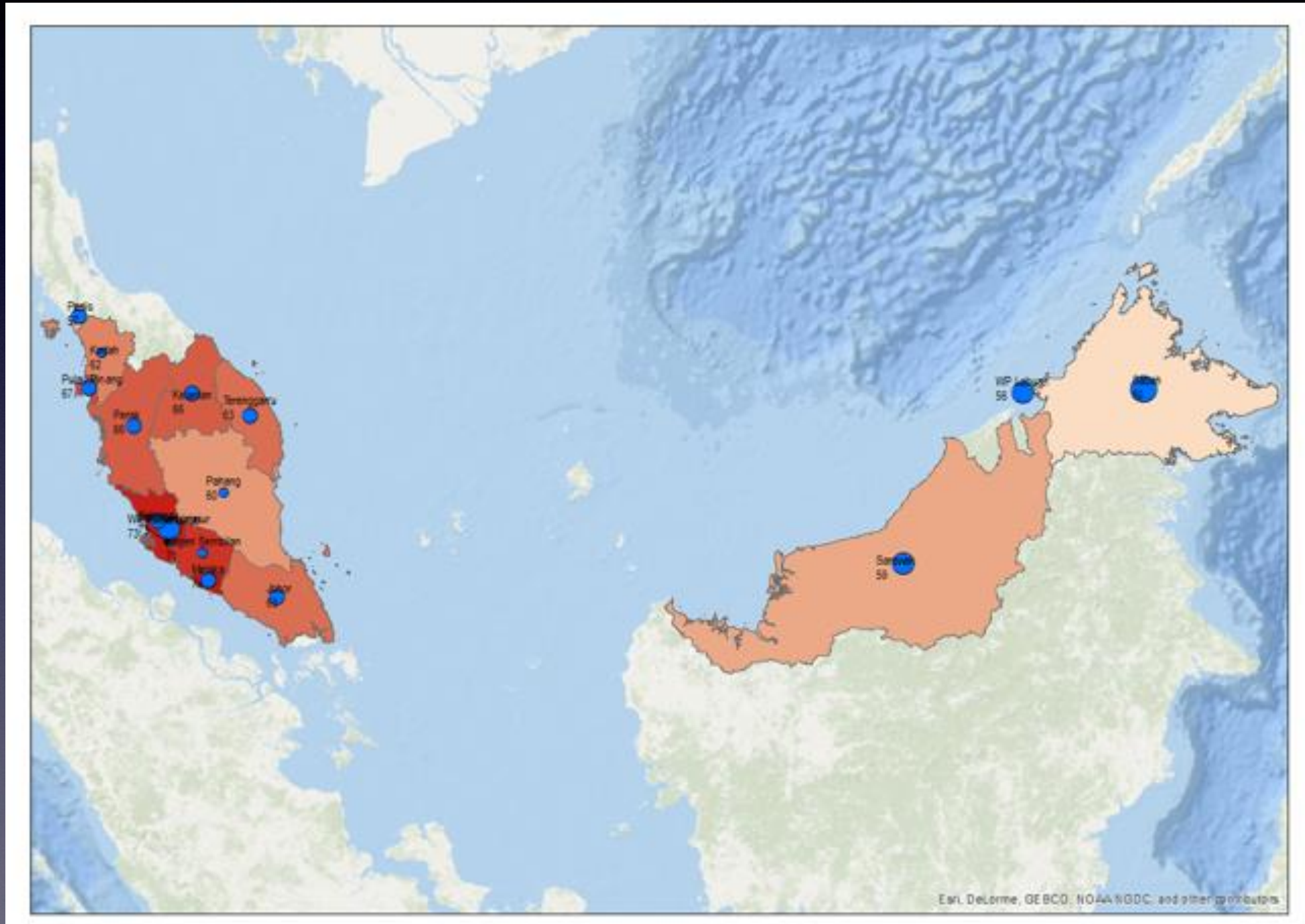


Figure 5: Incidence rates of TB and 2-year 95th-percentile of API.

Results

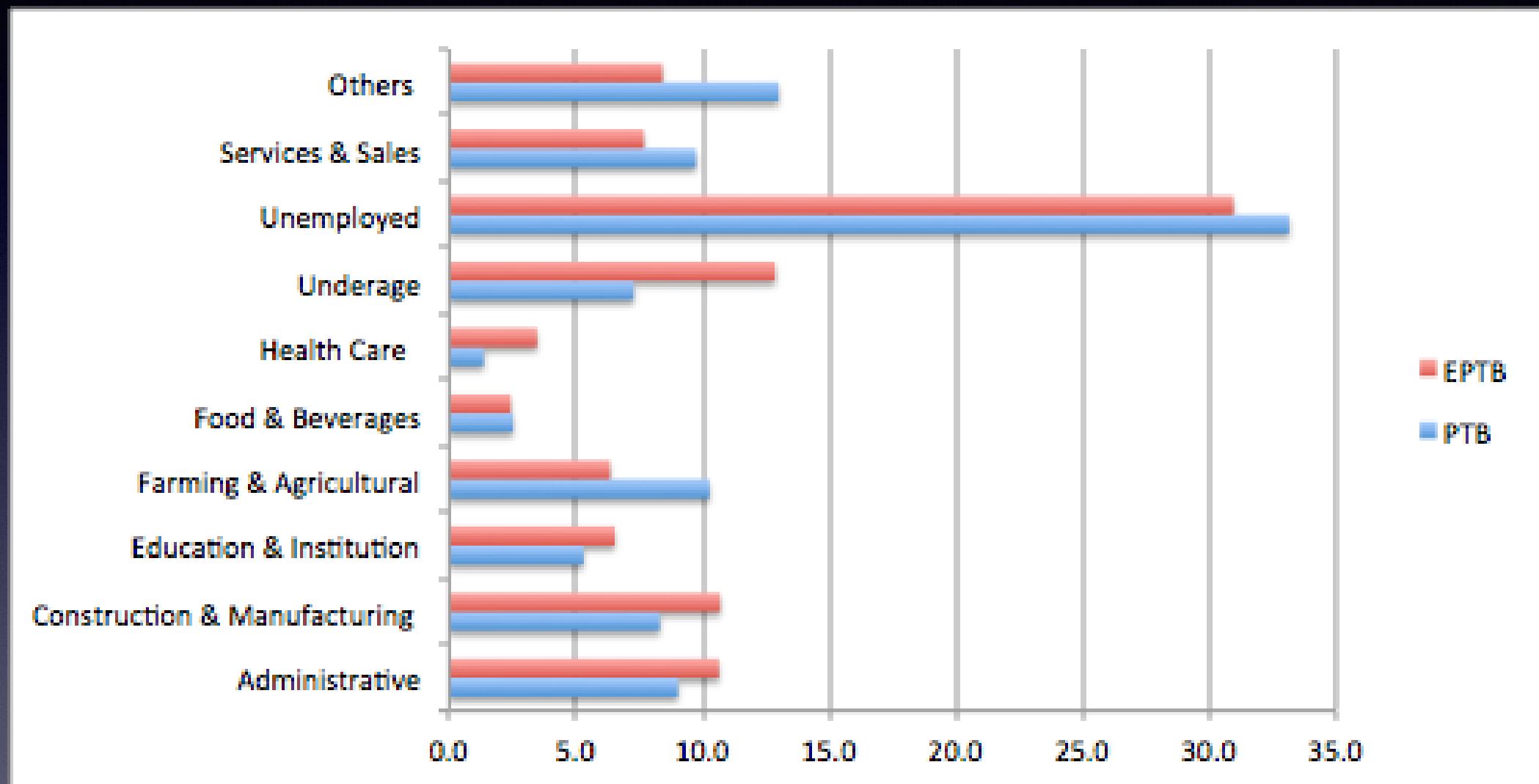
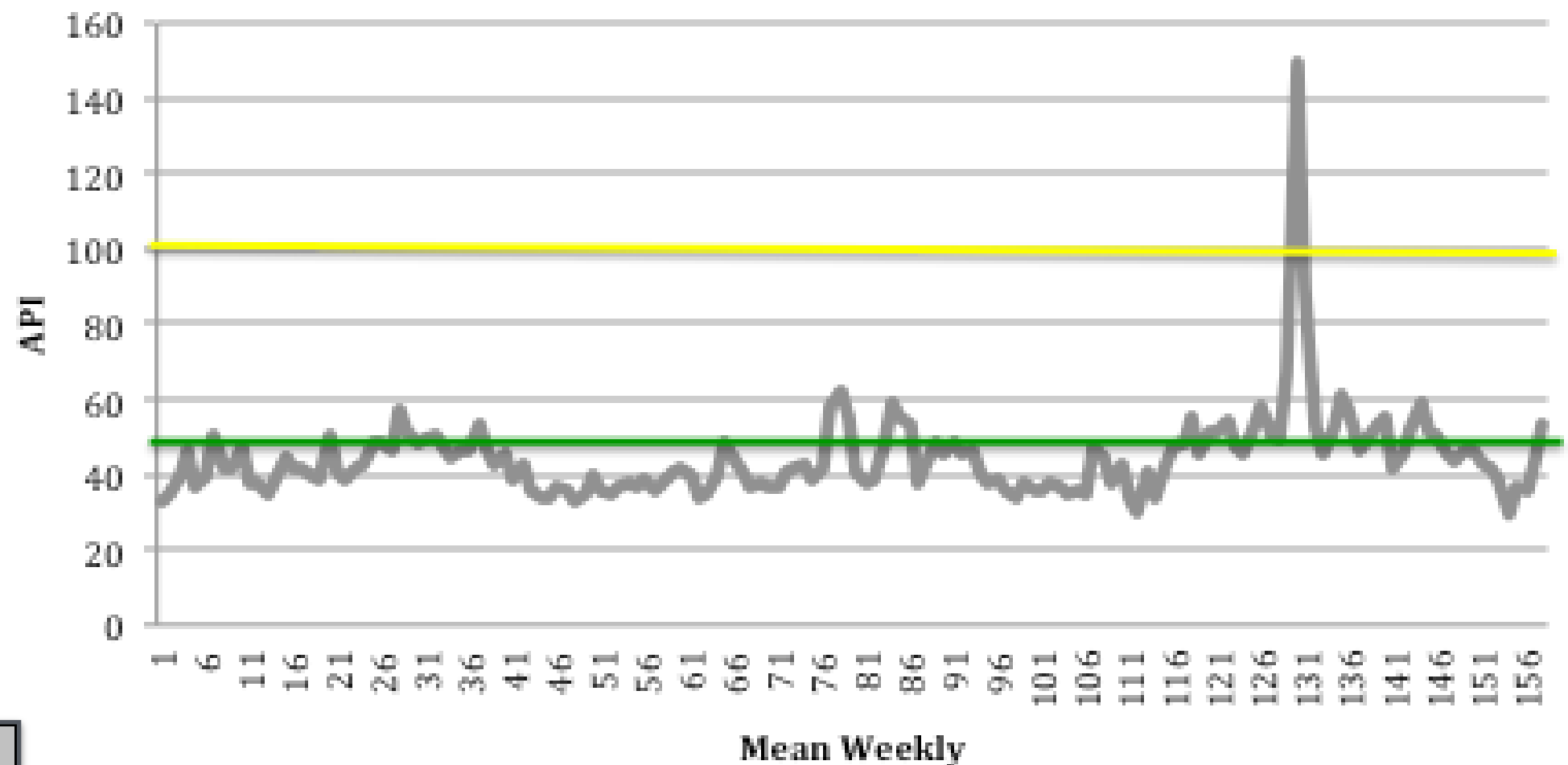


Figure 6: Employment and TB

PTB: Unemployed,
Services & Sales,
Agriculture.

EPTB: Children, HCW,
C&M, Administrative

Results



Malaysia's API

Air Pollution Index (API)	Air Quality Category	Color Code
0 – 50	Good	Green
51 – 100	Moderate	Yellow
101 – 200	Unhealthy	Orange
201 – 300	Very Unhealthy	Red
301+	Hazardous	Dark Red

Figure 7: Weekly Mean air pollutant index (API) from Jan 1, 2011 - Dec 31, 2013

Results

Table 1: The 2-year air pollutant concentrations profiles ($\mu\text{g}/\text{m}^3$).

Air Pollutant Exposure	Mean (SD)	Median (R)	5%	95%	Max
Air Pollutant Index (API)	45 (15.6)	20	22	65	
PM10 ($\mu\text{g}/\text{m}^3$)	43 (27.8)	38 (26)	15	89	995
O ₃ ($\mu\text{g}/\text{m}^3$)	33.2 (30.4)	25.5 (39.3)	2.0	92.3	323.9
CO ($\mu\text{g}/\text{m}^3$)	611.2 (459.18)	492.4 (435.2)	160.3	1465.9	13,112.5
SO ₂ ($\mu\text{g}/\text{m}^3$)	4.8 (7.4)	2.6 (2.6)	0	15.7	518.3
NO ₂ ($\mu\text{g}/\text{m}^3$)	17.77 (16.1)	13.17 (18.8)	1.9	50.8	238.9

Good

Moderate

Malaysia's API		
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Results

Table 2: Pearson correlation coefficients of the 2-year, 95th-percentile air pollutant concentrations

	API	PM10	SO ₂	NO ₂	O ₃	CO
API	1.0					
PM10	0.8685	1.0				
SO ₂	0.4227	0.4035	1.0			
NO ₂	0.6914	0.5245	0.6245	1.0		
O ₃	0.8559	0.5481	0.3962	0.6340	1.0	
CO	0.6891	0.6449	0.5918	0.9311	0.5172	1.0

Note: All coefficients were statistically significant at p-value < 0.05

Results: Crude analysis

Variable	PTB n (%)	EPTB n (%)	cOR (95% CI)	p-value
BCG scar*				
Yes	12,793 (75.7)	1,934 (81.5)	0.705 (0.632, 0.787)	< .001
No	4,111 (24.3)	438 (18.5)	1	
History of TB				
Yes	1,112 (6.6)	96 (4.0)	1.669 (1.349, 2.066)	< .001
No	15,792 (93.4)	2,276 (96.0)	1	
Crowding				
1 to 5	13,637 (85.9)	1,983 (87.9)	1	.040
6 to 10	2,005 (12.6)	252 (11.2)	1.157 (1.007, 1.330)	
> 10	236 (1.5)	22 (1.0)	1.560 (1.005, 2.421)	
Smoking Status				
Yes	5,905 (34.9)	488 (20.6)	2.073 (1.867, 2.301)	< .001
No	10,999 (65.1)	1,884 (79.4)	1	
Diabetes				
Yes	3,043 (18.0)	238 (10.0)	1.968 (1.712, 2.263)	< .001
No	13,861 (82.0)	2,134 (90.0)	1	

*BCG Scar indicates BCG vaccination status.

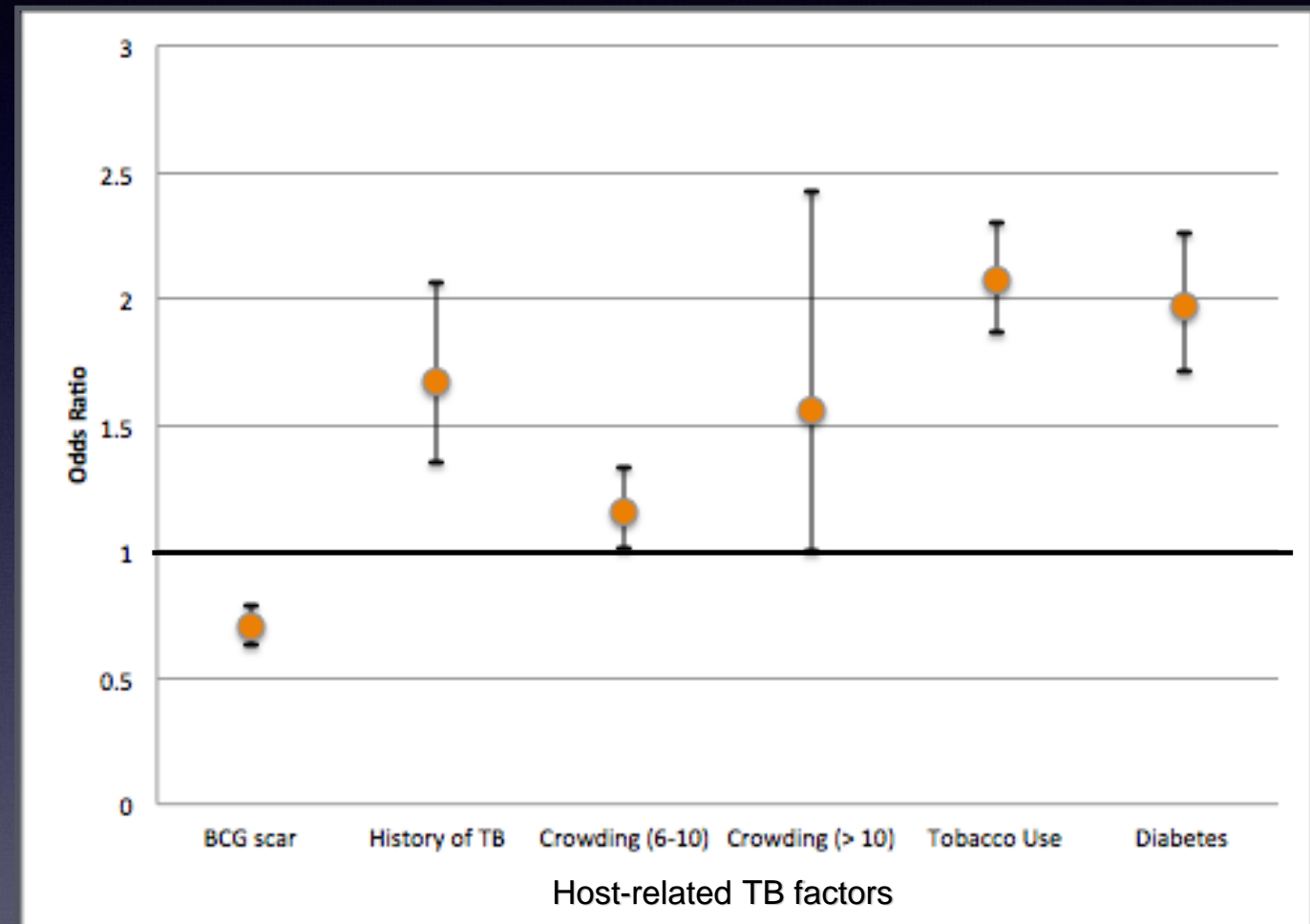


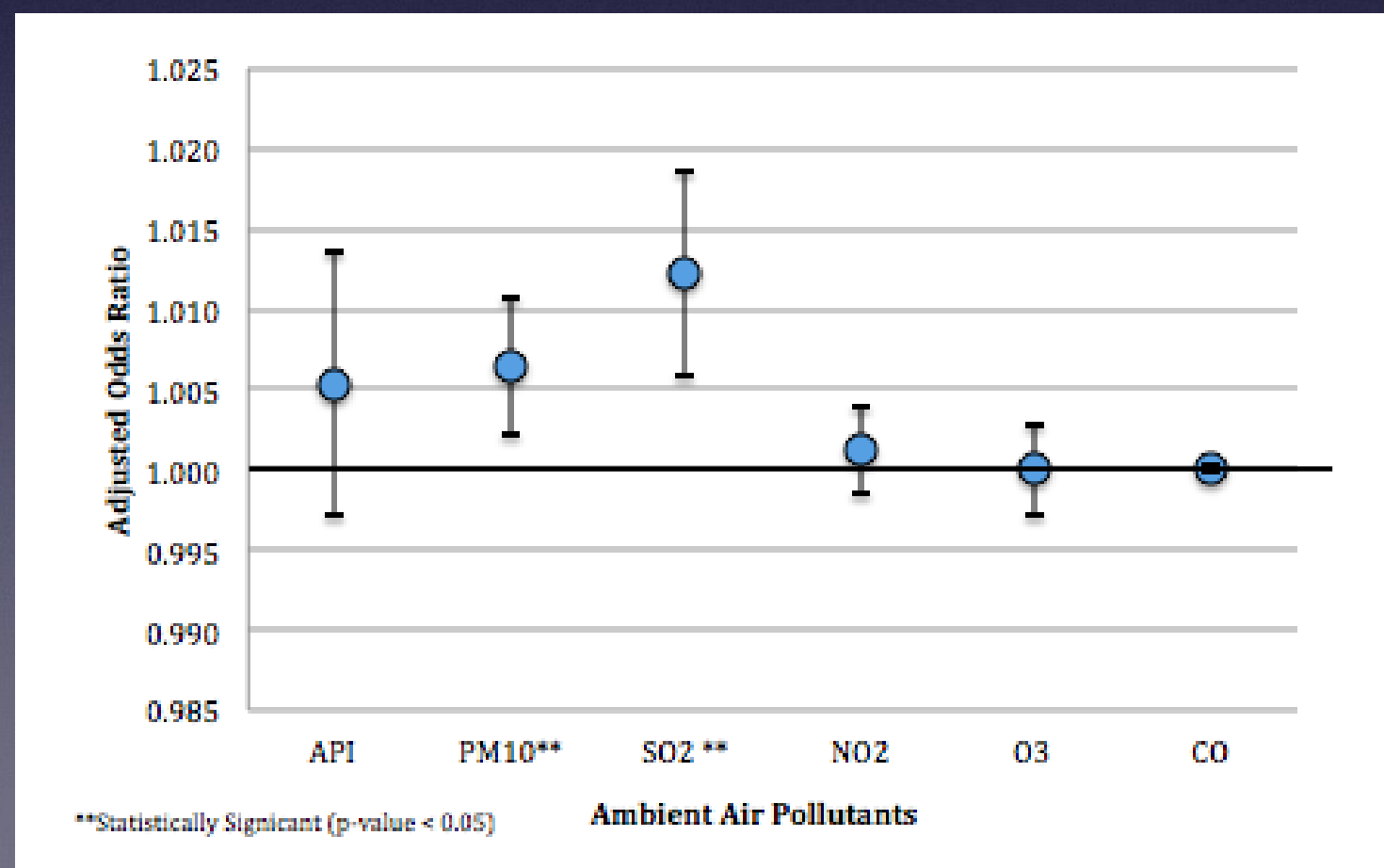
Figure 8: Logistic regression model estimated crude odds ratio (cOR) and 95% confidence intervals (CIs) for the associations of pulmonary TB and covariates (Host-related TB factors).

Results: Adjusted Analysis

Model (PTB=1, EPTB=0)	95 Percentile 2-year exposure	
	cOR (95% CI)	aOR* (95% CI)
API	0.993 (0.988, 0.998)	1.005 (0.997, 1.014)
PM10**	0.999 (0.997, 1.003)	1.006 (1.002, 1.011)
SO ₂ **	1.004 (0.999, 1.009)	1.012 (1.006, 1.019)
NO ₂	0.999 (0.996, 1.001)	1.001 (0.998, 1.004)
O ₃	0.996 (0.995, .998)	0.999 (0.997, 1.003)
CO	0.999 (0.999, 1.000)	1.000 (0.999, 1.000)

**Statistically Significant at p-value < 0.05

Figure 9: Logistic regression model estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of pulmonary TB and 95th-percentile in the estimates of ambient air pollutant concentrations for 2 years.



Discussion

1. 2-year 95th-percentile API was moderate;
 - No significant association with PTB* adjusted for covariates.
 - Other studies did not include API as an exposure variable.

Discussion: PM10

- Significant association with PTB* after adjusted for covariates.
- Corroborates with several study findings.
- PM10 increases the risk of infection; PTB outbreak episodes during dust storms in China.
- PM alters macrophages and causes inflammation ~ bacterial proliferations.
- In contrast with other study findings:
 - Ecological temporal study - PM10 not a significant predictor because [PM10] declined throughout their study period.
 - South Korea study - PM10 exceeded Korean National Air Standards and PM10 not a significant predictor when stratified by sex.

Discussion: SO₂

- Significant association with PTB* adjusted for covariates.
- Most studies - SO₂ respiratory morbidity and mortality, e.g London smog.
- Support findings in South Korea;
 - Males susceptible to PTB than females.
 - Postulates Interaction with Males' Lifestyles; Smoking, Alcohol use. (Did not control for other covariates)
- Affects synergistically with particulate matter - more toxic.
- A soluble gas and known as a respiratory tract irritant with little penetration to distal airways.
- Could decreased lung function; impairs mucociliary clearance and causes inflammation that could increase the risk of infection.

Discussion: NO₂, O₃, CO

- No significant associations with PTB* after adjusted for covariates ~ Cogent with other studies.
- Limited epidemiological or clinical evidence to support the effects of NO₂, Ozone and CO in human host-defense infection.
- Recognized as effect modifiers particularly for immunocompromized individuals (Asthma).
- The presence oxidants (reactive nitrogen species) as antimicrobial.
- Presence of NOX inhibits the proliferations and disease of intracellular mycobacterial.
- Ozone interacts synergistically with SO₂ that could cause severe lung functions than by itself but our study found that ozone and SO₂ had the weakest correlation.

Limitations

1. Controlling for Indoor air pollution - tobacco smoke variable;
 - Information from smokers only.
 - Underestimate for non-smokers.
2. Did not control meteorology variables: rainfall, temperature, humidity;
 - Potential effect modifiers.
3. EPTB as non-cases;
 - Better study design; Recruit healthy individuals as non-cases.
4. To include PM_{2.5} in future study.
5. Consider a study design with temporality.

Key Messages

- The grand 95th-percentile Air Pollutant Index (API) for two years: Moderate level.
- States with high incidences of TB have good levels 2-year 95th-percentile API than those states with the low TB incidence rates.
- Adjusted for covariates: API is not significantly associated with TB
- PM10 and Sulfur Dioxide have shown significant association with PTB.
- Covariates:
 - All host-related TB factors such as BCG vaccination protects against PTB.
 - History of TB, tobacco use, diabetes, ethnicity increased the odds of PTB in relative to EPTB.
- Adjusted for ambient air pollution, crowding and non-Malaysian were not associated with PTB.

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Terima Kasih



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Clean Air. Healthy Future.

UNITE TO  **END
TB**