

Tuberculosis and Alcohol use: Consumption and consumption

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Conflicts of Interest

- None

Objectives

- Review epidemiology of problem alcohol use and tuberculosis infection and disease
- Identify potential mechanisms by which alcohol impacts on tuberculosis progression and treatment response
 - Behavioral
 - Biologic

Two global epidemics

Tuberculosis

- TB is now the leading infectious disease killer globally
- Approximately 10.4 million individuals fell ill with TB, 1.7 million deaths in 2016

Alcohol abuse

- Alcohol major risk factor for death and disability globally, ranked 5th of 67 leading risk factors in 2010
- 3.3 million people die yearly due to harmful alcohol use, representing 5.9% of all deaths

About 10% of TB deaths globally have been attributed to alcohol as a risk factor

Major risk factors for TB

	Relative risk of active tuberculosis	Global prevalence rate (total population)	Population attributable factor (total population)*
HIV infection	26.7	0.8†	11.0
Malnutrition	3.2	16.7	26.9
Diabetes	3.1	5.4	7.5
Alcohol use >40 g/day	2.9	8.1‡	9.8
Smoking	2.0	26.5‡	15.8
Indoor air pollution	1.5	71.2	22.2

*Population attributable factor (percentage of tuberculosis cases attributable to the risk factor). †For 15-19 year age group. ‡For adults. Source: *Lancet* 2010; 375: 1814-29.

Table: Major risk factors for tuberculosis: weighted average for 22 high-burden countries

- Continued TB epidemic driven in part by comorbidities
- Urgent need to target modifiable risk factors
- In high income countries, diabetes and alcohol now thought to be more significant causes of immunological impairment than HIV due to prevalence

Not a new idea

- Benjamin Rush, the first US Surgeon General, observed >200 years ago that tuberculosis was more frequently encountered in those who had an affinity for alcohol
- >100 years ago William Osler also noted that alcohol was one of the greatest predisposing factors to the development of tuberculosis.

Increasing population-attributable fractions of TB deaths due to alcohol use, HIV-uninfected

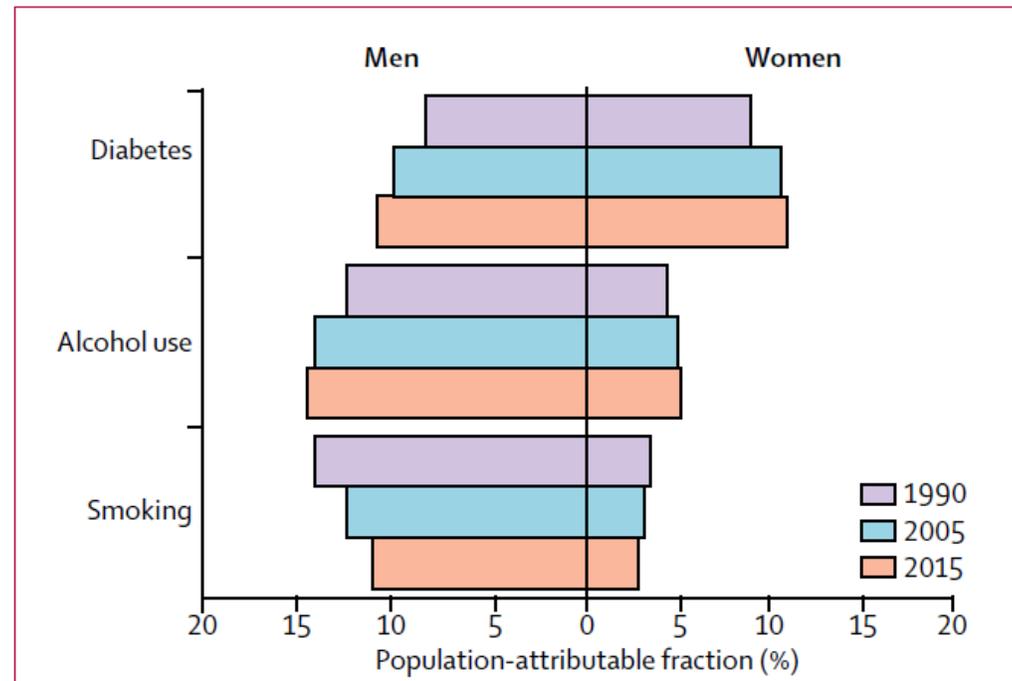
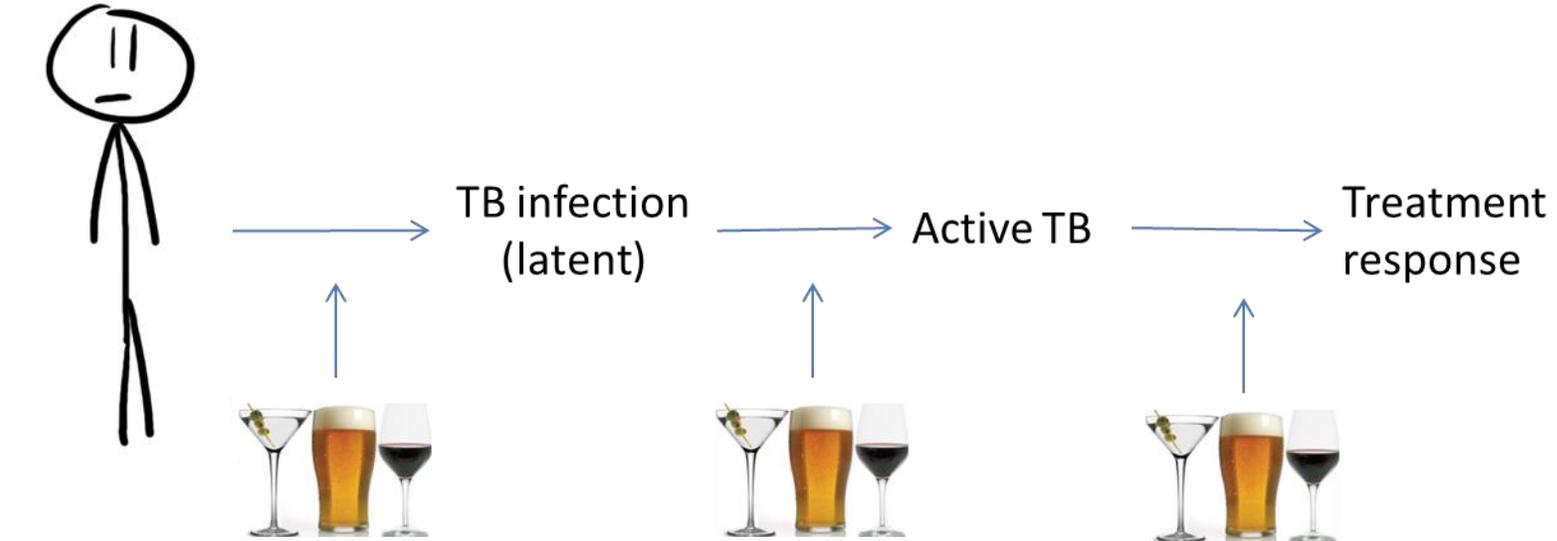
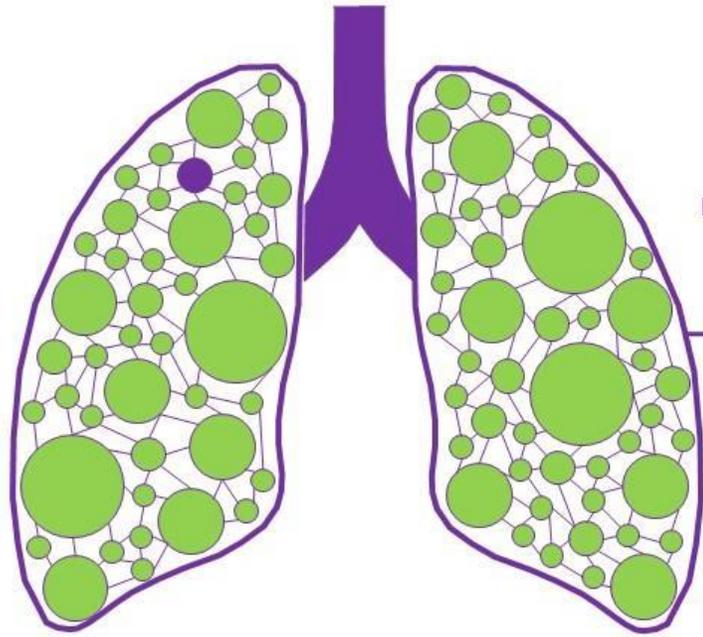


Figure 4: Age-standardised population-attributable fractions of tuberculosis deaths due to diabetes, alcohol use, and smoking among HIV-negative men and women in 1990, 2005, and 2015

Potentially modifies many steps





TRUST

THE TUBERCULOSIS TREATMENT
OUTCOMES & ALCOHOL USE STUDY



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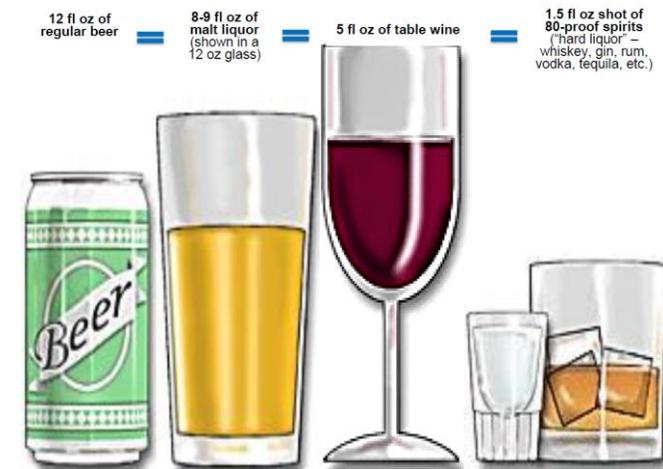
How define **problem alcohol use**



- Volume or pattern of alcohol consumption that results in adverse health events
- Amount consumed: abstainers, moderate, at-risk, heavy
- National Institute of Alcohol Abuse and Alcoholism (NIAAA) definitions
 - Drinking at low risk for developing alcohol use disorder:
 - For women, ≤ 3 drinks on any single day and ≤ 7 drinks per week.
 - For men, ≤ 4 drinks on any single day and ≤ 14 drinks per week.
 - Binge drinking: pattern of drinking that brings blood alcohol concentration to 0.08 g/dL
 - Typically occurs after 4 drinks for women, 5 drinks for men in 2 hours.
 - Occurred on at least 1 day in the past month.
 - Heavy alcohol use: binge drinking on 5 or more days in past month

How **measure** alcohol use (challenging)

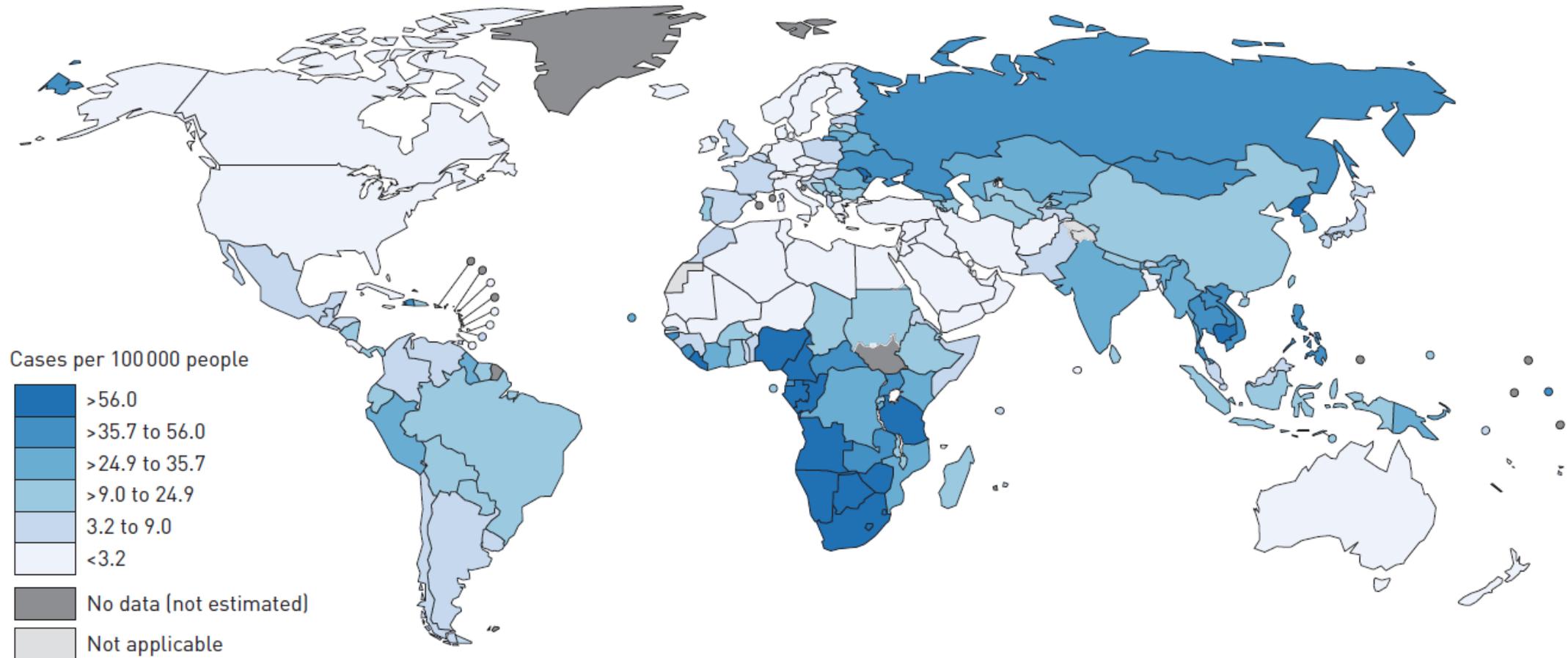
- Physician or provider report/identification
- Self report
 - What is a standard drink?
 - CAGE questionnaire
 - Alcohol Use Disorders Identification Test (AUDIT, AUDIT-C)
 - Time line follow back (TLFB)
- Biomarkers
 - Breath tests
 - Blood, Phosphatidylethanol (PEth) test
 - Urine
 - Hair sampling



Tuberculosis and alcohol co-prevalence

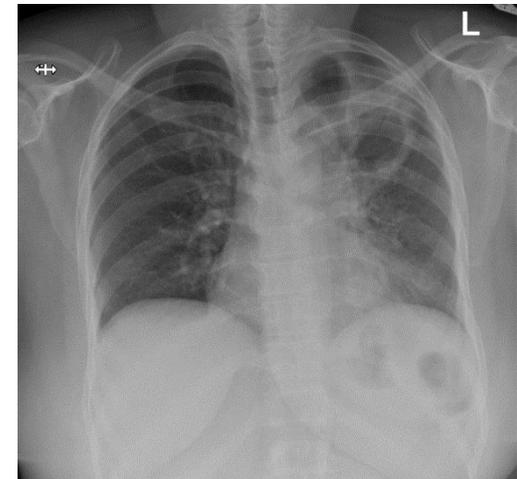
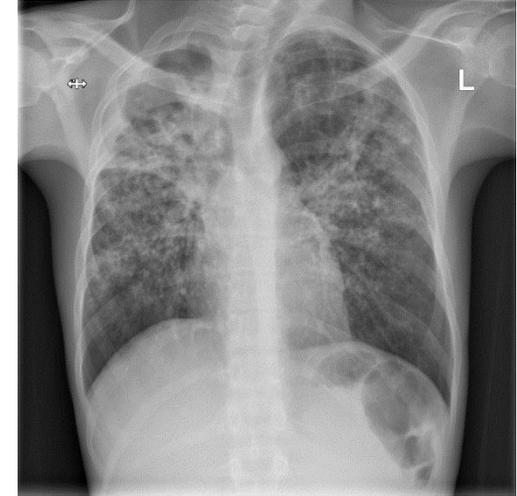
- Greater alcohol consumption is associated with **increased hazard** of progression from latent to active tuberculosis
- In the US, 1997-2012, **15% of all tuberculosis cases** and **25% of US-born tuberculosis cases** had documented excess alcohol use
- Globally, meta-analysis found alcohol is associated with a **35% higher risk of tuberculosis disease** compared to no alcohol use
 - risk of tuberculosis increased with the amount of ethanol intake (dose effect)

Estimated TB incidence rate per 100,000 persons attributable to alcohol consumption, 2014



Alcohol and clinical presentation of active tuberculosis

- In the US, patients with TB and excess alcohol use:
 - More **pulmonary** than extrapulmonary TB
 - + **sputum AFB smears**
 - More likely to have **cavitary disease**
 - **Lower culture conversion rates**
- Partially explained by association of alcohol use with delays in presenting for diagnosis and treatment
- Alcohol misuse appears associated with increased infectiousness

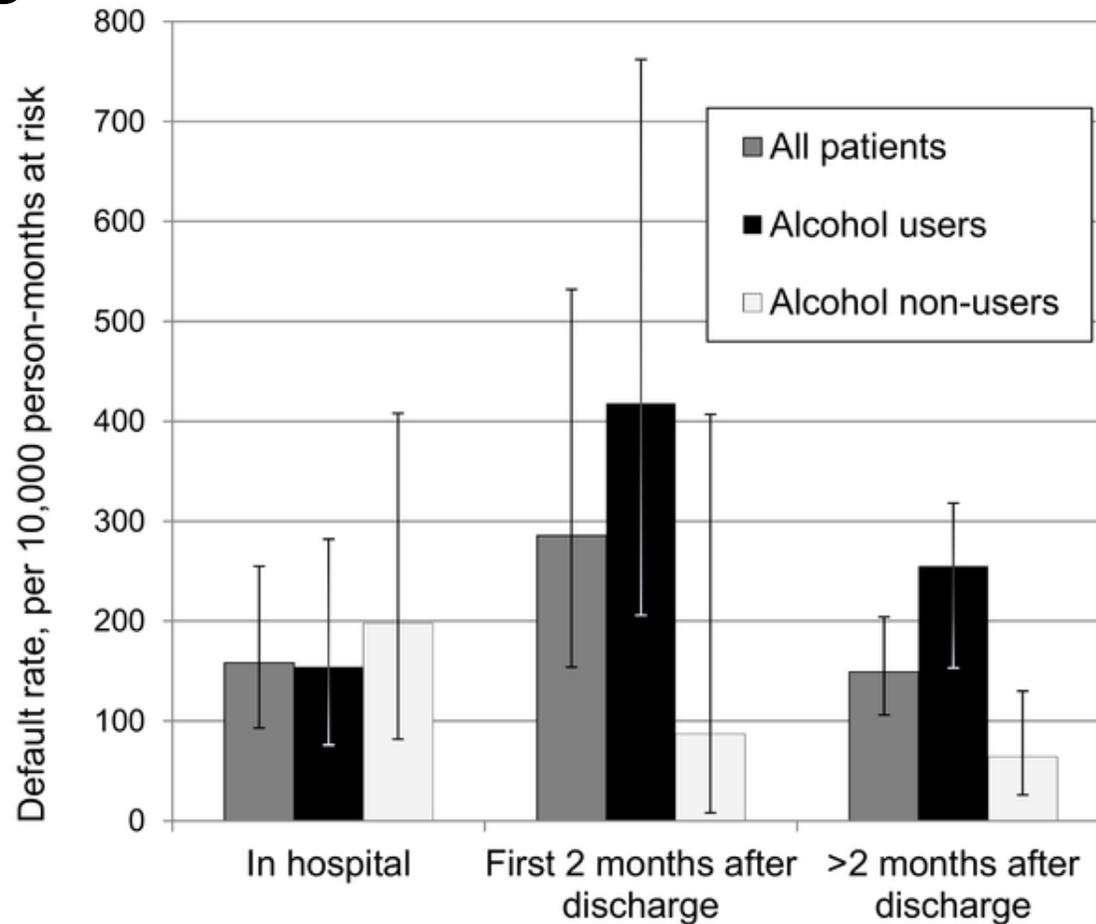


Alcohol and treatment outcomes: Loss to follow up

<u>Article</u>	<u>Study Design</u>	<u>Country</u>	<u>Finding</u>
Choi 2014	Prosp. cohort	S. Korea	OR 2.03 (1.27, 3.24)
Diel 2003	Prosp. cohort	Germany	AOR 5.96 (2.73, 13.02)
Kliiman 2010	Retro. cohort	Estonia	AOR 3.22 (1.93, 5.38)
Mutare 2011	Case control	Kenya	AOR 4.97 (1.56, 15.9)
Paixao 2007	Case control	Brazil	OR 4.67 (0.67, 40.14)
Salles 2004	Case-control	Brazil	OR 0.88 (0.24, 3.15)
Sendagire 2012	Prosp. cohort	Uganda	AOR 4.90 (1.80,13.50)
Lackey 2015	Prosp. cohort	Peru	AOR 2.22 (1.40, 3.52)
de Albuquerque 2007	Prosp. cohort	Brazil	OR 1.68 (1.07, 2.65)

- Most studies report association between alcohol use and loss to follow up
- A systematic review found a pooled odds ratio of **3.0 (95% CI: 1.8-5.0)** for alcohol dependence as a predictor of loss to follow up

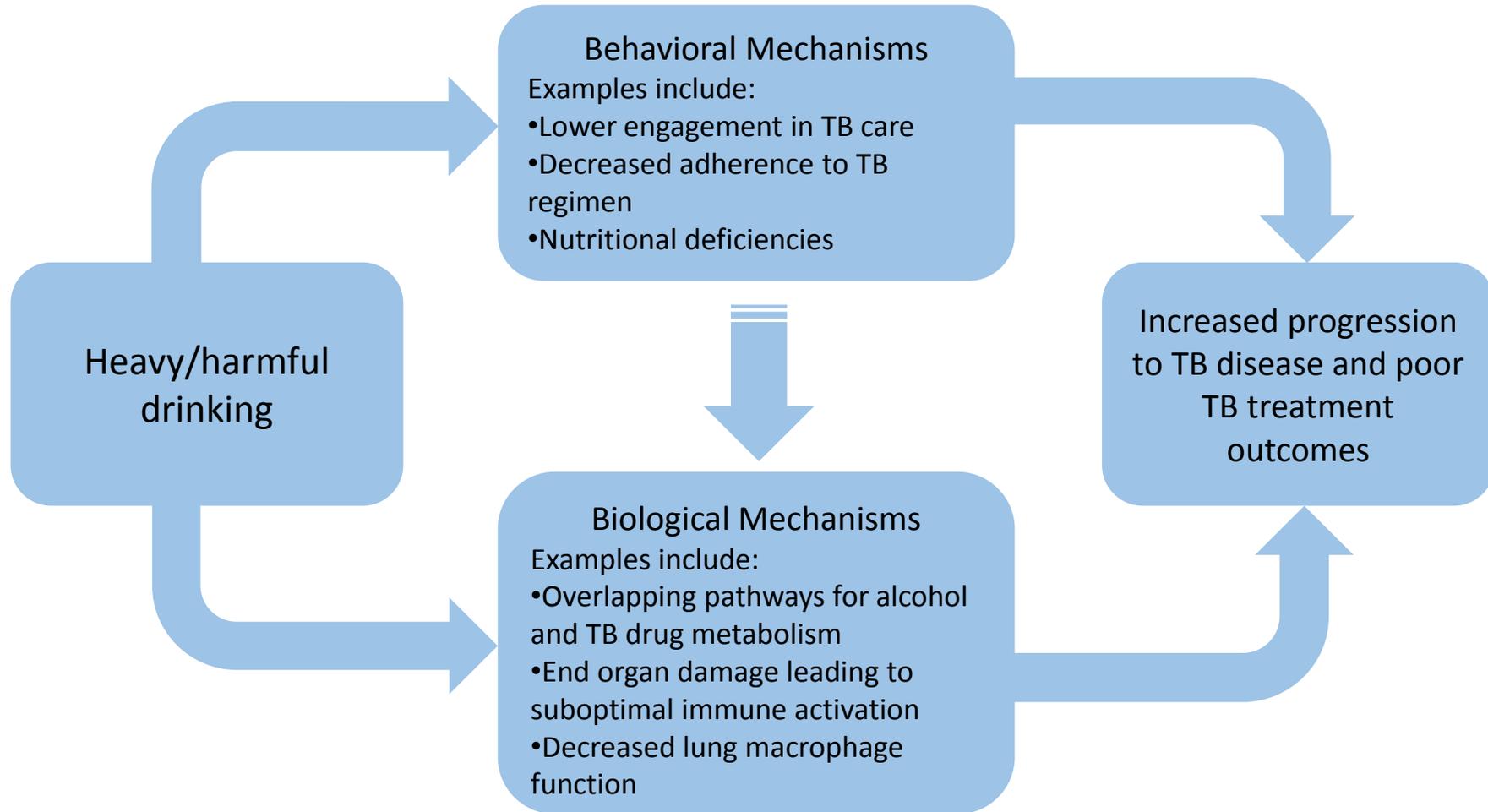
Default rates for patients on MDR-TB treatment, by time period and alcohol use status, Worcester, South Africa, 2007-2010



Alcohol and treatment outcomes: failure, death, or otherwise poor outcome

<u>Article</u>	<u>Study Design</u>	<u>Country</u>	<u>Outcome</u>	<u>Finding</u>
de Albuquerque 2007	Prosp. cohort	Brazil	Failure	AOR 2.78 (1.07, 7.18)
			Poor outcome	AOR 2.06 (1.32, 3.21)
Cayla 2009	Prosp. cohort	Spain	Death	OR 1.61
Millet 2011	Retro. cohort	Spain	Death	AHR 1.70 (1.2, 2.4)
Przybylski 2014	Retro. cohort	Poland	Poor outcome	AOR 1.84 (1.26, 2.67)
Reed 2013	Prosp. cohort	Korea	Death	AHR 0.36 (0.16, 0.78)
Magee 2015	Prosp. cohort	Georgia	Poor outcome	AOR 1.34 (0.48, 3.73)
Choi 2014	Prosp. cohort	S. Korea	Poor Outcome	AOR 1.10 (0.56, 2.19)

- Also appears association between problem alcohol use and failure, death



Behavioral-social cohorting places individuals at increased risk of acquisition

- Drinking venues as high risk sites for TB transmission

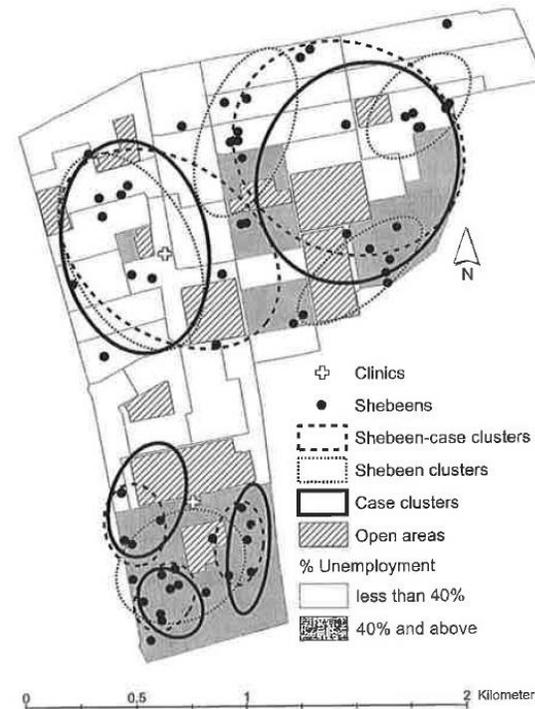
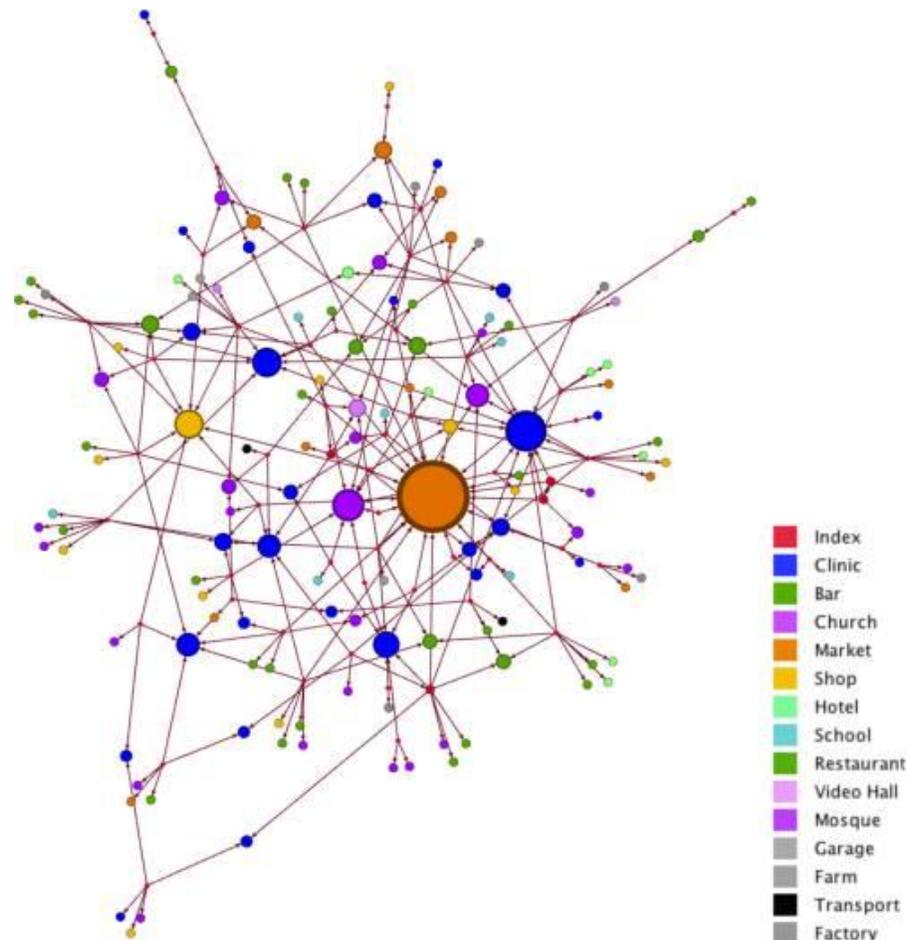
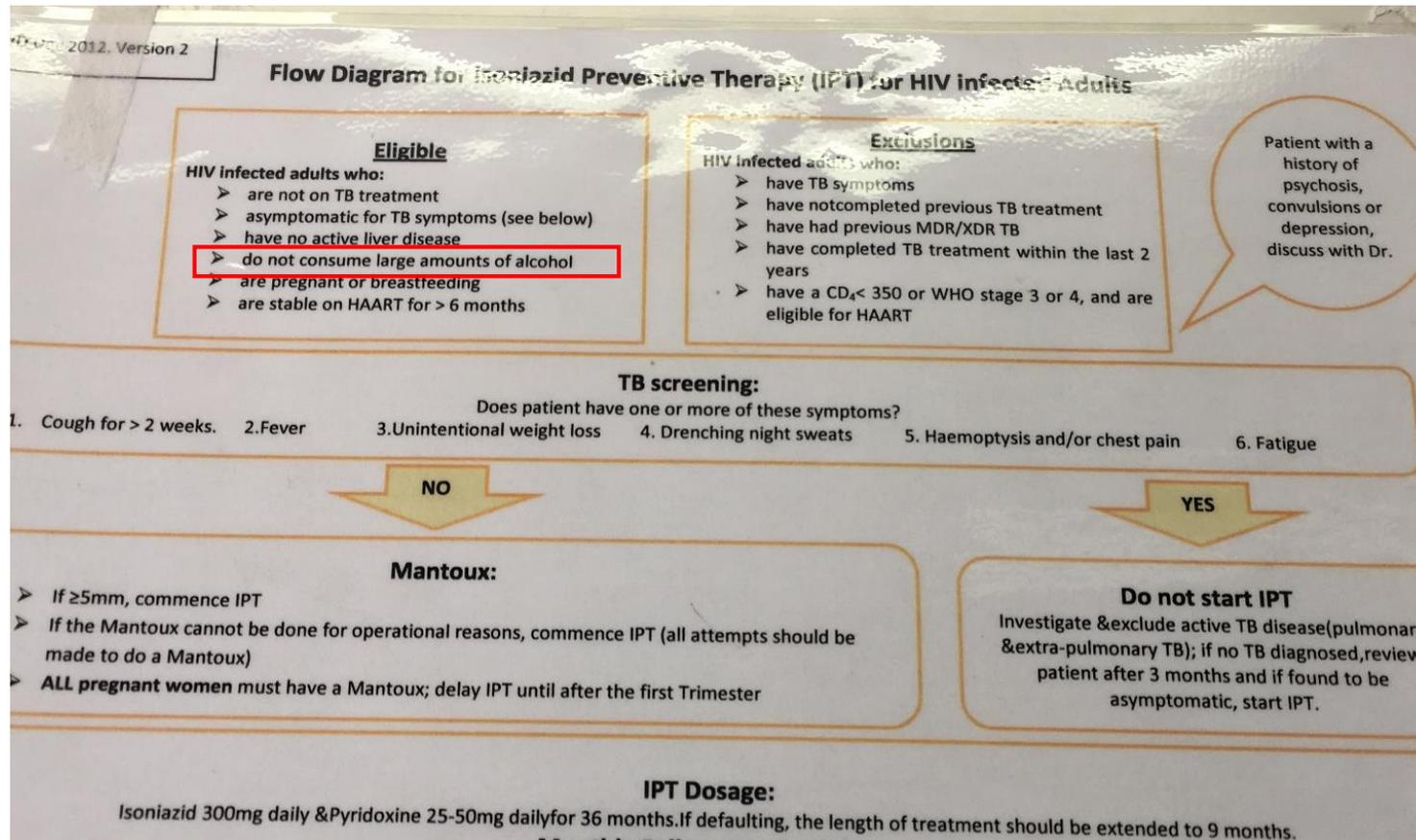


Figure 4 Geographical 'hot spots' of tuberculosis cases.

Behavioral-Physician prescribing practices and drug toxicity



- Exclude heavy alcohol drinkers, even those co-infected with HIV, from IPT (>25% sub Saharan Africa)
- Alcohol may increase risk of liver toxicity from TB meds by as much as 4-fold
- In Markov simulation model, we found 6 months IPT +ART benefit outweighed toxicity risk in India and Uganda, less in Brazil where lower TB incidence

Behavioral- problem alcohol use impacts care retention and adherence to TB treatment (latent and active)



- PREVENT TB Trial, LTBI treatment in US and Canada: noncompletion due to adverse events higher in men who reported use or abuse of alcohol (1.6 or 2.2 times higher, $p=0.03$, $p=0.01$) compared to men without alcohol. Noncompletion due to other reasons 2 times higher in individuals with alcohol abuse compared to none ($p<0.001$)
- Data from South Africa show an association between heavy alcohol use and missed DOTS visits and TB treatment non adherence
- Alcohol use is an independent risk factor for loss to follow up from MDR TB therapy
- Benefit of DOT to keep those with alcohol problems in care

Behavioral- Interventions to address alcohol use during tuberculosis care

1. Screening and brief intervention (discussion and pamphlet) for alcohol in 3 public clinics South Africa. 4880 individuals with TB, 24.6% tested positive for the AUDIT.
 - Did not find reduction in alcohol consumption due to intervention; found some reduction in controls
2. Looked at feasibility and assessed effectiveness of 2 alcohol interventions-brief counseling intervention and naltrexone- for patients with AUDs and TB in Tomsk Oblast, Russia.
 - Did not find a significant impact on TB or alcohol outcomes.
 - Those with prior attempts to quit drinking benefitted more from naltrexone than the general group (already in a contemplative state, lower average amount alcohol consumed per day)—led to exceptional TB outcomes (92.3% favorable)
3. In Chennai, India, found brief intervention of individualized counseling at 0, 2, 4, 6 months (randomized to zones), led to more favorable TB outcomes (87% vs 62%, OR 3.9 p=0.04; 6% loss to follow up in intervention vs 35% in control arm).
 - Movement to lowest AUDIT risk in both arms (89% in intervention vs 40% in controls).
 - Raising attention to alcohol leads to benefit in both groups, although vulnerable to social desirability via self report
 - Participatory design

Biologic- Alcohol's effects on TB drug concentrations

- Increased acetylation in rat liver cells in the presence of ethanol, potentially leading to an increased metabolism rate
- The few studies on isoniazid PK in those with problem alcohol use have shown mixed results regarding the effect on isoniazid maximal concentrations and half life
- In TB patients experiencing poor treatment outcomes, researchers found increased rifampicin levels among those who reported drinking more than one alcoholic drink/day.
- Higher drug levels or more adverse events may further contribute to poor outcomes via withdrawal of particular drugs or death.

Biologic- Alcohol's effects on TB drug concentrations

- Problem alcohol use has been associated with acquisition of drug resistant TB (primarily isoniazid and rifampin resistance), which may reflect a failure to attain optimal drug levels.
- In Indonesia, MDR-TB was found to be associated with excessive alcohol use.
- In Russia, TB patients admitted to hospitals had an 8-fold increased likelihood of TB drug resistance if they had an alcohol use disorder history .
- A study in the Baltic region found alcohol abuse conferring a 3.5-fold increased odds of acquiring multi- and extensively drug-resistant TB.

Biologic-Alcohol and the immune system

- Animal models have provided evidence of chronic alcohol use modulating the immune system's ability to fight tuberculosis infection.
- Mice that consumed ethanol before BCG vaccination were not protected against Mtb inoculation, had reduced IFN- γ and IL-2 production in regional lymph nodes, though interestingly mice consuming ethanol after BCG vaccination did not show impaired protection.
 - This raises the question whether chronic alcohol use's impact on immunity to tuberculosis may not extend to immunity established prior to the start of alcohol use.
- The CD4+ cells of alcohol-consuming mice show diminished capability to secrete IFN- γ when stimulated with Mtb compared to normal controls.
- In addition to altered T cell function, there is also evidence for impaired T cell recruitment. CD8+ cells were diminished in lung-associated lymph nodes of alcohol-consuming mice when compared to control mice inoculated with Mtb.

Biologic-Alcohol and the immune system

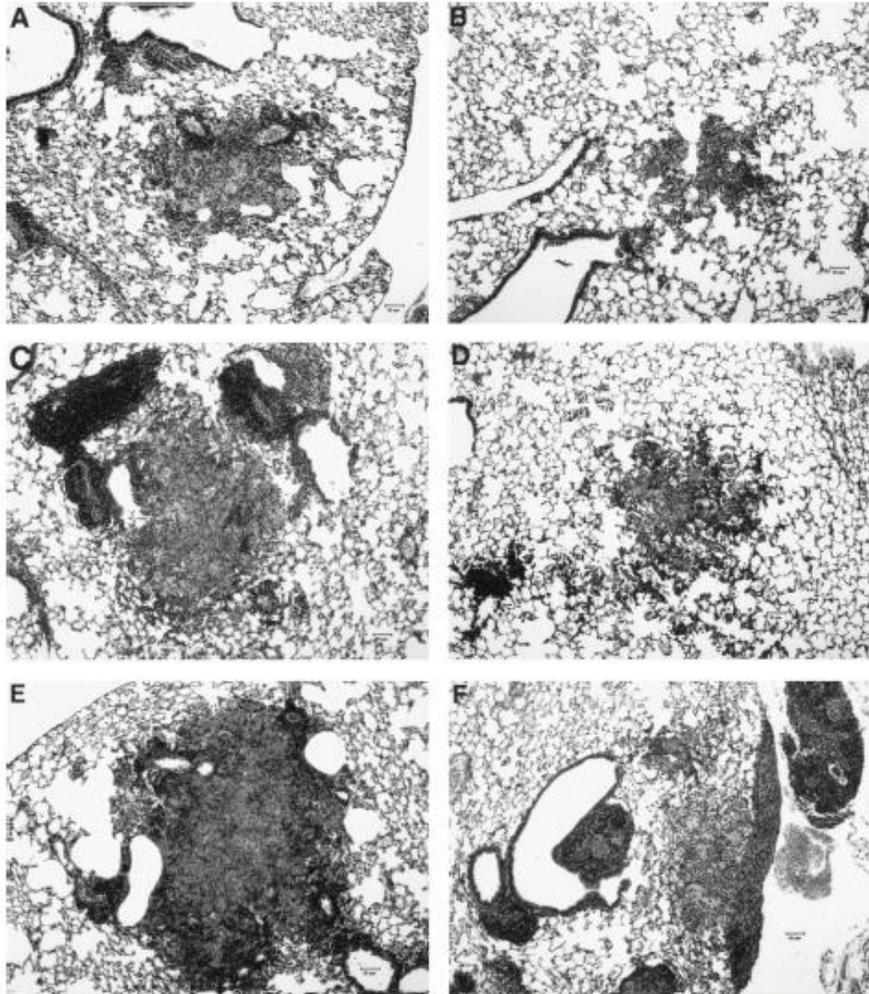
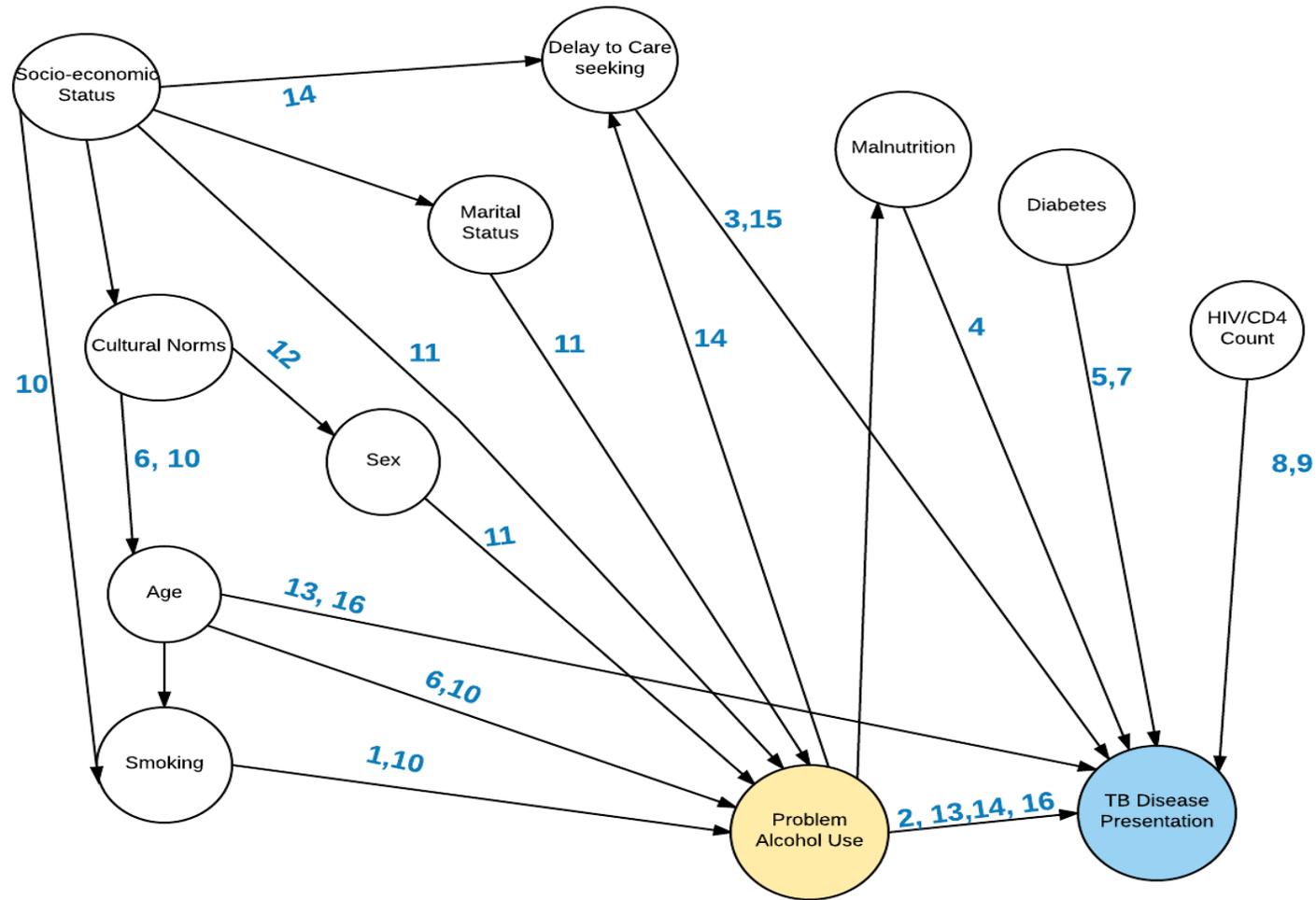


FIG. 6. Representative lung sections from mice in the LCD and LED groups stained with hematoxylin and eosin. All magnifications, $\times 100$. (A) Day 21 LCD mouse; (B) day 21 LED mouse; (C) day 28 LCD mouse; (D) day 28 LED mouse; (E) day 35 LCD mouse; (F) day 35 LED mouse.

- Alcohol-consuming mice have shown to have significantly higher pulmonary Mtb burden and impaired granuloma formation, approximately one-third smaller than controls.

Complicated



Modern tuberculosis epidemic



“I am happy here, we have a full day and there are lots of talks on substance abuse and about families” ES, 39, she has 4 children incl. daughter who is in the Pediatric Ward. As an MDR TB patient whose sputum is not yet negative she cannot visit her daughter in the same hospital. Her husband is in the TB hospital too. Her extended family is looking after her other children. Her parents work on fruit farms and she works in a vegetable packing factory when not in hospital.

Thank you!!

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