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Tuberculosis research has seen an exciting resurgence in basic, clinical and systematic reviews that affect clinical practice. This issue deals with groundbreaking work in the past year that has led to a WHO endorsement of a new diagnostic tool worldwide (Xpert MTB/RIF) for TB and MDR and a negative endorsement for another commonly utilized hospital based diagnostic TB test (commercial serology). Likewise, a better understanding of TB epidemiology necessitates the reexamination of conventional wisdom, including the natural course of non-HIV TB as well as the interplay between tobacco, diabetes and BMI. Better basic research tools has led questions about the major role of non-compliance in MDR TB and pharmacokinetic variability and the combination of basic whole genome sequencing and social network analysis to identify sources of TB outbreaks. We also reviewed three clinical trials on preventive therapy for TB, HIV and the multi-country study on FDCs in pulmonary tuberculosis.

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Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis

Authors: Chang K, Lu W, Wang J et al.
URL: http://dx.doi.org/10.1016/j.jinf.2012.02.012
Comments: This is one of the first published systematic reviews on the rapid diagnosis of tuberculosis (TB) and rifampicin resistance, Xpert MTB/RIF assay using PCR technology. The objective of the systematic review was to establish the diagnostic accuracy of Xpert (Cepheid) MTB/RIF assay in pulmonary TB. From a total of 90 studies identified in Pubmed and Embase databases, 18 studies satisfying the major quality criteria (QUADAS) were subsequently analyzed. Overall, 10,224 suspected of having TB specimens were included, 2983 were from patients with bacteriologically confirmed TB, 6183, non-Tb specimens and 335 clinical TB specimens (those responding to anti-Tb medications with TB clinical and radiologic findings, no microbiological confirmation). Fifteen out of the 18 included studies estimated the diagnostic accuracy of Xpert MTB/RIF in pulmonary TB. The 15 studies showed significant heterogeneity and thus the random effects model approach was used.

The overall pooled sensitivity of 15 studies was 90.4% (95% CI 89.2%-91.4%), pooled specificity was 98.4% (95% CI 98.0-98.7), the diagnostic odds ratio (DOR) was 328.3 (95% CI 154.3-698.3) and the area under the summary ROC curve (AUC) was 0.9822. For rifampicin resistance, the over-all pooled sensitivity was 94.1% (95% CI 91.6%-96.0%), pooled specificity was 97.0% (95% CI 96.0-97.7%), pooled DOR was 177.8 (95% CI 41.7-757.7) and AUC was 0.9832. Results in 4 studies for TB with HIV co-infection also had high specificity (98%) but lower sensitivity (81.7%), DOR of 217 and for 7 studies extra-pulmonary TB even lower results (specificity 86.1%, sensitivity 80.4, DOR 59.2).

The authors conclusions were that TB and rifampicin–resistance can be rapidly and effectively diagnosed with Xpert MTB/RIF assay.

The authors cited possible publication from the analysis of the funnel plots but this was offset by the use of Beggs’s test and Egger’s test and the high QUADAS (quality) scores of the studies included. It would also have been useful if the authors had mentioned the prevalence of TB (high- or low prevalence or even income levels) in the studies included. An ongoing Cochrane review will help validate this study.

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http://www.wiley.com/bw/vi.asp?ref=1323-7799&site=1
Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: an updated systematic review and meta-analysis

Authors: Steingart KR, Flores LL, Dendukuri N et al.
URL: [http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001062](http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001062)

Comments: An updated systematic review from a 2006 review and updated to June 2010 was done to assess the diagnostic accuracy of commercial serological tests for pulmonary and extra-pulmonary TB with a focus on the relevance of these tests in low and middle-income countries. Methods recommended by the Cochrane Collaboration and GRADE approach for rating quality of evidence were utilized. They pre-specified subgroups to address heterogeneity and summarized test performance using bivariate random effects meta-analysis. For pulmonary TB, 67 studies were included (48% form low-to middle-income countries) with 5,147 participants.

For all tests, estimates were variable for sensitivity (0-100%) and specificity (31-100%). For anda-TB IgG, the only test with enough studies for meta-analysis, pooled sensitivity was 76% (95% CI 63-87%) in smear-positive (seven studies) and 59% (95% CI 10-96%) in smear-negative (four studies) patients. Pooled specificities were 92% (95% CI 74-98%) and 91% (95% CI 79-96%) respectively. Compared with ELISA (pooled sensitivity 60% [95%CI 6-65%] pooled specificity 98% [95% CI 96-99%]), immunochromatographic tests yielded lower pooled sensitivity 53% [95%CI 42-64%] and comparable pooled specificity 98% [95% CI 94-99%]. For extra-pulmonary TB, 25 studies were included (40% for low- and middle-income countries) with 1,809 participants, for all tests estimates were widely variable for sensitivity (0-100%) and specificity (59-100%). Overall quality of evidence for studies of pulmonary and extra-pulmonary TB was graded very low. Findings from this systematic review were inputted to a cost-effectiveness study of serological testing in India. In comparison with sputum microscopy, serological testing resulted in fewer DALYs averted, more false-positive diagnoses and secondary infections while increasing costs to the Indian TB control program 4-fold.

Conclusions: Despite expansion of the literature since 2006, commercial serological tests for TB continue to produce inconsistent and imprecise sensitivity and specificity among all categories of patients. Quality of evidence remains very low.

WHO recently issued a negative advisory against the routine use of commercial serological tests for TB. Based on this review article there is no clear evidence of its validity and accuracy given the imprecision and questions of quality studies.

Respirology
May 2012 issue now online:
Three months of rifapentine and isoniazid for latent tuberculosis infection

Authors: Sterling TR, Villarino E, Borisov AS, et al.
Comments: The authors conducted an open-label, randomized, non-inferiority clinical trial comparing 3 months of directly observed once-weekly combination therapy with rifapentine (900 mg) plus isoniazid (990 mg) in 3986 subjects versus standard 9 months self-administered daily isoniazid (300 mg) in 3745 subjects. Subjects enrolled were from the United States, Canada, Brazil, and Spain and followed for 33 months. Modified intention-to-treat analysis was conducted showing 0.19% developed TB in the combination group against 0.43% in the standard isoniazid. There was also a statistically significant difference in the rates of treatment completion (82.1% versus 69.0%, P<0.001) between the two groups and rates of permanent drug discontinuation owing to adverse events were 4.9% in the combination group and 3.7% in isoniazid-only group (P=0.0009). Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7%, respectively. (P<0.001). The authors concluded that the use of rifapentine plus isoniazid weekly for 3 months was as effective as 9 months daily isoniazid in preventing tuberculosis and had a higher treatment-completion rates and similar adverse events.

New regimens to prevent tuberculosis in adults with HIV infection

Authors: Martinson NA, Barnes GL, Moulton LH et al.
Comments: The preventive study was done in South Africa involving 1148 adults with a median age of 30, HIV infection (median and CD4 cell count of 484/mm³) and positive tuberculin skin test not taking antiretroviral therapy. Patients were randomized to receive rifapentine (900 mg) plus isoniazid (900 mg) weekly for 12 weeks, rifampicin (600 mg) plus isoniazid (900 mg) twice weekly for 12 weeks, isoniazid daily for up to 6 years (continuous isoniazid) or isoniazid (300 mg) daily for 6 months (control group). Incidence rates for active tuberculosis were 3.1/100 person-years in the rifapentine-isoniazid group, 2.9/100 person-years in the rifampin-isoniazid group, 2.7/100 person-years in the continuous isoniazid group as compared to 3.6 per 100 person-years in the control group (P>0.05 for all comparisons). Serious adverse reactions were more common in the rifampin-isoniazid group. Two of the 58 isolates of M. tuberculosis (3.4%) were found to have multi-drug resistance. The adherence to treatment was lowest in the control group (83.8%) compared to more than 90% for rifapentine combination (95.7%), rif-isoniazid (94.8%) and 89.1% for continuous INH. Conclusions: On the basis of the expected rates of TB in the study population of HIV-infected adults, all secondary prophylactic regimens were effective. Neither 3-month course of intermittent rifapentine or rifampicin with isoniazid was superior to 6 months of isoniazid.

This study on HIV patients on preventive TB therapy adds to the evidence of the safety and efficacy of shorter, intermittent regimens involving rifapentine, rifampin and isoniazid among HIV patients. There was however no calculation for statistical difference in adherence in the study (95.7% and 94.8% in rifapentine-isoniazid and rif-INH versus 83.8% in INH) which may also partly contribute to the difference between control and comparator groups and no mention whether DOT or similar treatment adherence strategies were utilized in either arms.
Efficacy and safety of a 4-drug fixed dose combination (FDC) regimen compared with separate drugs for treatment of pulmonary tuberculosis. The study C randomized controlled trial.

Authors: Lienhardt C, Cook SV, Burgos M. et al.
URL: http://jama.ama-assn.org/content/305/14/1415.full.pdf+html

Comments: The Study C Trial was a parallel group open-label, non-inferiority, randomized controlled trial in 11 sites in Africa, Asia and Latin America between 2003 to 2008, involving 1585 adults with newly diagnosed smear-positive pulmonary tuberculosis given 4 drugs (rifampicin,isoniazid,pyrazinamide,ethambutol) as an FDC (n=798 patients), or separately (n=787) in the 8-week intensive phase of treatment. Favorable response was defined as negative culture result at 18 months post-randomization and per protocol analysis as well as modified intention-to-treat analysis utilizing 2 models were utilized. Results showed, per-protocol analysis, 555 of 591 (93.9%) had a favorable outcome in the FDC group versus 548 of 579 (94.6%) in the separate-drugs group (risk difference -0.7% [90% CI -3.0-1.5%]. In the model 1 analysis, 83.3% had a favorable outcome in the FDC group against 84.8% in the separate drugs group (risk difference -1.5% [90% CI -4.7-1.8%]. In the post hoc model 2 analysis, 89.8% in the FDC and 91.0% had favorable outcomes (risk difference -1.2% [90% CI -3.9-1.5%]. Adverse events were similarly distributed among treatment groups. Compared with a regimen of separately administering drugs, a 4-drug FDC regimen satisfied pre-specified non-inferiority criteria in 2 of 3 analyses. Although the results do not show full non-inferiority of the FDCs compared to separate drugs using the strict definition applied in this trial, use of FDCs is preferred because of its inherent advantages.

One disadvantage noted by the authors is the tendency for clinicians to completely discontinue FDCs in the presence of adverse drug events over the separate drugs group which may have accounted for some of the outcomes. Likewise, the use of FDCs rifampicin and isoniazid in both treatment groups during the continuation phase made this not a true head to head comparison between FDCs and loose tablets. The use of stricter criteria of fulfilling 3 analyses in this study which is a novelty made the conclusions more robust but similar criteria are not widely used in clinical trials evaluation.

Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modeling analysis

Authors: Basu S. Stuckler D. BVitton Asaf. et al.
URL: www.bmj.com/content/343/bmj.d5506.full

Comments: The authors constructed a state transition, compartmental, mathematical model of tuberculosis epidemics to estimate the impact of alternative future smoking trends on tuberculosis control. TB incidence, prevalence and mortality in each WHO region from 2010-2050 and incorporated changing trends in smoking, case detection, treatment success and HIV prevalence were utilized. The model predicted that smoking would produce an excess of 18 million TB cases (SE 16-20) and 40 million deaths from TB (39-41) between 2010-2050, if smoking continues along current trajectories. The effect of smoking was anticipated to increase TB cases by 7% (274 million vs 256 million) and deaths by 66% (101 million vs. 61 million) compared with model predictions that did not account for smoking. Smoking was also expected to delay the millennium development goals (MDGs) to reduce TB deaths by half between 1990 t0 2015. The authors conclude tobacco smoking could substantially increase TB cases and deaths worldwide in the coming years undermining progress towards TB mortality targets. Aggressive tobacco control could avert millions of deaths from TB.

An interesting study and reference for clinicians, policy makers, TB and tobacco-prevention advocates on the higher risk of TB for smokers and implications on worldwide mortality if this is not addressed soon.
Natural history of tuberculosis: duration and fatality of untreated PTB in HIV negative patients: a systematic review

Authors: Tiemersma EW van der Werf Nj, Borfdorff MW et al.
URL: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017601
Comments: To estimate the duration and case fatality of untreated pulmonary tuberculosis in HIV negative patients, the authors reviewed studies from the pre-chemotherapy era. Untreated smear-positive cases among HIV-negative individuals has a 10-year-case fatality rate variously reported between 53 and 86% with a weighted mean of 70%. Ten year case fatality rate of culture positive smear negative cases was nowhere reported directly but can be indirectly estimated to be approximately 20%. The duration of onset to cure or death is approximately 3 years and appears to be similar for smear-positive and smear-negative tuberculosis.

Conclusions: Current models of untreated tuberculosis that assume a total duration of 2 years until self-cure or death underestimate the duration by one year but the case-fatality estimates of 70% smear-positive and 20% smear-negative appears to be satisfactory.

Conventional wisdom and TB lore has always pegged death rates or cure at 2 years, this study provided new information on the natural history of TB that this has been underestimated by a year. The problem with the study is the difficulty of obtaining primary data, the use of different types of information sources (cohort, prevalence and incidence studies, notification and mortality rates and prevalence and mortality rates). The authors admitted their initial Medline searches were negative for eligible studies and so had to resort to snowball sampling, secondary analysis and interview with experts. Likewise the authors correctly identified the difficulties conducting a study such as this including the assumptions, absence of consideration of risk factors among others, variability across countries, etc as well as poor quality studies in the earlier decades and the absence of the rigor and high standards of the published literature today.

Whole-genome sequencing and social-network analysis of a tuberculosis outbreak

Authors: Gardy, JL. Johnston JC. Ho Sui, SJ. et al.
Comments: An outbreak of TB occurred over a 3-year period in a medium-size community in British Columbia, Canada. The results of the mycobacterial interspersed repetitive unit-variable- number tandem-repeat (MIRU-VNTR) genotyping suggested the outbreak was clonal. Traditional contact tracing did not identify the source, the authors used whole-gene sequencing and social-networking analysis in an effort to describe the outbreak dynamics. The authors sequenced the complete genome of 32 M. Tb outbreak isolates and 4 historical isolates (samples from the same region but before outbreak). Epidemiologic and genomic data were overlaid on a social network constructed by means of interviews with patients.

Whole-genome data revealed 2 genetically distinct lineages of M. tb with identical MIRU-VNTr genotypes, suggesting 2 concomitant outbreaks. Through integration of large-scale bacterial whole-genome sequencing and social-network analysis, the study showed that a socio-environmental factor—most likely increased crack cocaine—triggered the simultaneous expansion of two extant lineages of M. tuberculosis that was sustained by key members of a high-risk social network. Genotyping and contact tracing alone did not capture the true dynamics of the outbreak.

This article showed that traditional contact tracing has limitations and new approaches including this social network questionnaire maybe better to identify sources of outbreaks and maybe useful even for MDR and XDR cases.
**Nutrition, diabetes and tuberculosis in the epidemiological transition**

**Authors:** Dye C Trunz BB Lonroth K et al.

**Reference:** PLoS One 2011; 6:e21161


**Comments:** Diabetes prevalence and body mass index (BMI) reflect the nutritional profile of populations but have opposing effects on tuberculosis (TB) risk. Interactions between diabetes and BMI could help or hinder TB control in growing, aging, urbanizing populations. The authors compiled data describing temporal changes in BMI, diabetes prevalence and population age structure in rural and urban areas for men and women in countries with high (India) and low (Rep. Korea) TB burdens. Using published data on the risks of TB associated with these factors, the authors calculated expected changes in TB incidence between 1998 and 2008. In India, TB incidence cases would have increased (28% from 1.7 m to 2.1 m) faster than population size increase in TB incidence per capita of 5.5% in 10 years. In India, general nutritional improvements were offset by a fall in BMI among the majority of men living in rural areas. The growing prevalence of diabetes in India, increased the annual of TB cases in people with diabetes by 46% between 1998 and 2008. In Korea, by contrast, the number of TB cases increased more slowly (6.1% from 40,200 to 42,800) than the population size (14%) because of positive effects of urbanization, increasing BMI and falling diabetes prevalence. Consequently, TB incidence per capita fell by 7.8% in 10 years. Rapid population aging was the most significant adverse event in Korea.

**Conclusions:** Nutritional and demographic changes had stronger adverse effects on TB in high-incidence India than in lower-incidence Korea. The unfavorable effects in both countries can be overcome by early drug treatment but, if left unchecked, could lead to an accelerating rise in TB incidence. The prevention and management of risk factors for TB would reinforce TB control by chemotherapy.

**With recent studies showing the high correlation to TB risk as well as poor treatment outcomes related to co-morbidities such as diabetes and malnutrition, this study adds to the current knowledge as the lifestyle diseases and disease of poverty intersect. However, studies such as this can also have to consider confounding variables besides the factors sighted (population size, BMI, diabetes etc).**
Multidrug-Resistant Tuberculosis not due to noncompliance but between-patient pharmacokinetic variability

Authors: Srivastava S, Pasipanodya JG, Meek C et al.
Reference: J Inf Diseases 2011; 204:1951-9
URL: http://jid.oxfordjournals.org/content/204/12/1951.long

Comments: Conventional wisdom holds that non-adherence is the proximate cause of multi-drug resistance. The level of non-adherence associated with emergence of MDR-TB is unknown. Performing a randomized controlled trial in which some patients would be randomized to non-adherence would be unethical; therefore other study designs should be utilized. The authors performed hollow fiber studies for both bactericidal and sterilizing effects, with inoculum spiked with 0.5% rifampin and isoniazid resistant isogenic strains in some experiments. Standard therapy was administered daily for 28-56 days, with extents of non-adherence varying between 0-100%. Sizes of drug-resistant populations were compared using analysis of variance. The authors also explored the effect of pharmacokinetic variability on MDR-TB emergence using computer-aided clinical trial simulations of 10,000 Capetown, South Africa, tuberculosis patients.

Therapy failure was only encountered at extents of non-adherence ≥ 60%. Surprisingly, isoniazid and rifampin-resistant populations did not achieve ≥ proportion in any experiment and did not achieve a higher proportion with non-adherence. However, clinical trial simulations demonstrated that approximately 1% of tuberculosis patients with perfect adherence would still develop MDR-tuberculosis due to pharmacokinetic variability alone.

Conclusions. These data, based on a preclinical model, demonstrate that non-adherence alone is not a sufficient condition for MDR tuberculosis emergence.

A thought-provoking study (sure to elicit controversy from the title alone) using for the first time, an in-vitro model, the hollow fiber system to evaluate the forgiveness (defined as the difference between the medications post-dose duration of beneficial action and the prescribed dosing interval). Plainly defined forgiveness is directly related to the number of doses that can be skipped without causing detectable disease relapse or recurrence (from editorial accompanying article)

Interestingly, none of the non-adherence schemes mimicked led to drug-resistance, challenging the widely accepted belief that MDR-TB is caused by non-adherence and pointing to the pharmacokinetic variability as possibly the more important cause. This study challenges conventional wisdom and its conclusions need to be further validated by further basic and clinical research.