# Australian

# Tuberculosis Review

## July 2018

## Conferences

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**Editorial Group**

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## Contents:

## Editorial

In the latest edition of the Communicable Diseases Intelligence,  Bastian et al from the National Tuberculosis Advisory Committee  present their recommendations on the use  of IGRAs and TST In the diagnosis of tuberculosis infection and disease.  Sensibly they have found no place for such testing in disease with perhaps the exception of small children.  Neither the TST nor IGRA tests are capable of predicting which  reactor will develop disease.  Indeed there is greater discordance between the results of the different tests in children.   The group felt that TST was superior in serial testing of health care workers, because positive         IGRAs sometimes reverted to negative. The report did not mention that old tuberculin in the Prophit study sometimes did the same. It is known that an IGRA is the test of choice for those who had received BCG and that both tests may be preferable in those about to start immunosuppressive treatment or biologics, .  It is disappointing that use of both tests concurrently is not recommended for everyone being screened.

## Population studies

**Tuberculosis in Far North Queensland , Australia: a retrospective clinical audit.**

**Wilson et al    Cairns, Qld, Australia**

**Intern Med J    2018; June 5: 13994**

**Background:**  Compared with global numbers, Australia has enjoyed relatively good tuberculosis control over the last thirty years with an annual incidence of 5.7 per 100,000 population.  Thanks to its unique geography  and proximity to high burden countries such as Papua New Guinea (PNG), Far North Queensland (FNQ)  has previously been

shown to have higher rates of tuberculosis compared with both the state and national average.

**Aims:** Document tuberculosis epidemiology in FNQ with comparison to two previous audits of the region.

**Methods:** Retrospective clinical audit of all cases of tuberculosis notified to the Cairns Tuberculosis Control Unit between 2006 and 2016.

**Results**: 453 cases were identified, 374 with microbiological/histological confirmation . There were 312 cases of pulmonary tuberculosis; 155 extrapulmonary; and 21 disseminated. Three quarters (327/453 were identified in the overseas-born population. Of the remaining 40 were Torres Strait origin and 19 Aboriginal Australians. Where drug susceptibility was known, two-thirds (247/368) were fully sensitive, 42 mono-resistant, 78 multidrug –resistant and one extensively drug resistant. Rates of HIV co-infection were less than 3% (10/362)

**Conclusions:** Tuberculosis remains a significant problem in FNQ. Case numbers have increased three-fold since the 1990s. Much of the increase comes from the overseas-born population. Although PNG accounts for the majority , the number of positive notifications amongst those born elsewhere has increased five-fold since 2010. Tuberculosis amongst Aboriginal Australians has decreased following policy changes in response to previous audits. Tuberculosis in Torres Strait residents, however, has increased from 12 cases (1993-2002) to 40 (2006-2016).

**Comment**: Are the Torres Strait islanders developing disease from more contact with their PNG visitors or does the increasing rate of diabetes in the islanders play a role?

## Household-contact investigation for detection of tuberculosis in Vietnam.

**Fox et al   Sydney, NSW, Australia; Hanoi, Ho Chi Minh City, Vietnam; Paris, France.**

Background: Active case finding is a top priority for the global control of tuberculosis, but robust evidence for its effectiveness in high-prevalence settings is lacking. We sought to evaluate the effectiveness of household-contact investigation, as compared with standard passive measures alone, in Vietnam.

Methods: We performed a cluster-randomized, controlled trial at clinics in 70 districts (local government areas with an average population of approximately 500,000 in urban areas and 100,00 in rural areas) in eight provinces of Vietnam. Health workers at each district clinic or hospital were assigned to perform either household contact intervention  plus standard passive case finding alone (control group). In the intervention districts, household contacts of patients with positive results for tuberculosis on sputum smear microscopy (smear-positive tuberculosis) were invited for clinical assessment and cheat radiography at baseline and at 6,12,24 months. The primary outcome was the cumulative incidence of registered cases of tuberculosis among household contacts of patients with tuberculosis during a 2 year period.

Results: In 70 selected districts, we enrolled 25,705 household contacts of 10,964 patients who had smear-positive pulmonary tuberculosis. In the 36 districts that were included in the intervention group, 280 of 10,096 contacts were registered as having tuberculosis (1788 cases per 100,000 population) as as compared with 110 of 15,638 contacts ( 703 per 100,000 population) in the control group (relative risk of the primary outcome in the intervention , 2.5; 95% CI 2.0 to3.2; P<0.001}; the relative risk smear positive disease among household contacts in the intervention group was 6.4 (95%CI 4.5 to 9.0; P<0.001

**Conclusions:** Household-contact investigation plus standard passive case finding was more effective than standard case finding  for the detection of tuberculosis in a high-prevalence setting at 2 years.

**Comment:** It is interesting that the number of family members in these Vietnamese households is surprising small.

<div align="right">JT</div>

## Tuberculosis-United States, 2017

**Stewart et al   CDC, Atlanta, GA, USA**

**Abstract:** In 2017, a total of 9,093 cases of tuberculosis (TB) were provisionally reported in the United States, representing an incidence rate of 2.8 cases per 100,000 population. The case count decreased by 1.8% from 2016 to 2017 and the rate declined by 2.5%  over the same period. These decreases are consistent with the slight decline in TB seen over the past several years.. This report summarizes the provisional TB surveillance data reported to CDCs National Tuberculosis Surveillance System for 2017 and in the last decade. The rate of TB among non-US-born persons was 25 times the rate among US-born-persons. Among non-US-born persons, the highest TB rate among all racial/ ethnic groups was among Asians (27 per 100,000 persons),  followed by non-Hispanic blacks (blacks ,22.0). Among US-born persons, most TB

cases were reported among blacks (37.1%), followed by non-Hispanic whites (whites 29.5%). Previous studies have shown that the majority of TB cases in the United States are attributed to reactivation of latent TB infection (LTBI) Ongoing efforts to prevent TB transmission and disease in the United States remain important to continued progress toward TB elimination. Testing and treatment of populations most at risk for TB disease and LTBI, including persons born in countries with high TB prevalence and persons in high-risk congregate settings are major components of this effort.

**Comment:** Why is the US ahead not only in terms of TB control than Australia, but also speed in reporting the data?

# Pharmacology

**Total synthesis of ecumicin**

**Hawkins et al Sydney, NSW, Australia**

**Org Lett 2018;Feb 7**

**Abstract:** The first total synthesis of the potent anti-mycobacterial cyclic depsipeptide natural product ecumicin is described. Synthesis was achieved via solid-phase strategy. Incorporating the synthetic non-proteinogenic amino acids M-methyl-4-methoxy-1-tryophan and threo-beta-hydroxy-1-phenylalanine into the growing linear peptide chain. The synthesis employed key on-resin esterification and dimethylated steps as well as a final macrolactamization between the unusual N-methyl-4-methoxy-tryptophan and a bulky N-methyl-1 valine residue. The synthetic natural product possessed potent antimycobacterial activity against the virulent H37rv strain of Mycobacterium tuberculosis,
**Comment:** Let us hope that such synthesis will make the drug cheaper to produce, when it becomes available.

<div align="right">JT</div>

# Tuberculosis Infection

**Barriers to treatment adherence for individuals with latent tuberculosis infection: a systematic search and narrative synthesis of the literature.**

**Liu et al Seattle, Wa, USA; Hamilton, Ontario, Canada; Manchester, UK; Sydney, NSW, Australia.**

**Int J Plann Manage 2018**

**Objectives:** We investigated the rates of initiation and completion of treatment for latent TB infection (LTBI), factors explaining non adherence and interventions to improve treatment adherence in countries with low TB incidence.
**Design**: A systematic search was performed in PubMed and Embase. All included articles were assessed for risk of bias. A narrative synthesis of the results was conducted.
**Results:** There 54 studies included in the review. The proportion of people initiating treatment varied from 24% to 98% and the proportion of people completing treatment varied from 19% to 90%. The main barriers to adherence included the fear or experience of adverse effects, long duration of treatment, financial barriers, lack of transport to clinic (for patients) and insufficient resources for LTBI control. While interventions like peer counseling, incentives and culturally specific case management have been used to improve adherence, the proportion of people who initiate and complete LTBI treatment remains low.
**Conclusion:** To further improve treatment and LTBI control and to fulfill the World Health Organisation goal of elimination TB in low incidence countries, greater priority should be given To the use of treatment regimens involving shorter durations and fewer adverse effects, like the 3 month regimen of weekly rifapentine plus isoniazid, supported by innovative patient education and incentive strategies.
**Comment:** Yes , but there will still remain people from certain cultures who cannot be convinced that use of drugs when they are symptomatic, will not disturb the balance of nature.

<div align="right">JT</div>

**Screening and treatment rates for latent tuberculosis among newly-arrived refugees in an urban facility in Connecticut.**

**Duchen et al New Haven CT, USA**

**Conn Med 2017;81:291**

**Abstract:** There is a high prevalence of latent tuberculosis infection (LTBI) and risk of reactivation among refugees. This study describes LTB prevalence, treatment initiation, and completion rates rates seen at one urban Connecticut hospital . This retrospective chart review includes 248 adult refugee patients screened between January 2009 and April 2012. Demographics, tuberculin skin test results (TST) results, treatment initiation and c0omplion rates and treatment-related variables

were collected. Ninety eight percent of adult refugees received TST screening and 44.0% were diagnosed with LTBI. Of these, 95.5% initiated treatment and of those 48.2 % completed treatment. Early treatment discontinuation was high , with 29.5% of patients diagnosed with LTBI defaulting after the fist clinic visit. Despite near universal screening within this refugee population , LTBI treatment initiation and completion rates remain low. Greater efforts should be made to ensure LTBI treatment initiation and completion among refugees through early case management and shorter treatment duration.

**Comment:** This report may be over one year old but I believes it summarises the situation in Australia. If default is early even the new 3 month regimen may not solve the problem.

<div align="right">JT</div>

# Molecular studies

**Genome-wide analysis of multi-and extensively drug –resistant Mycobacterium tuberculosis.**

**Coll et al London, Liverpool, Hinxton, UK; Thuwal, Makkah, Saudi Arabia; Sydney, NSW, Melbourne, Vic, Australia; Porto, Lisbon, Portugal; Salvador, Brazil; Ho Chi Minh city, Vietnam; Mumbai, India; Karonga, Malawi; Cape Town, Tygerberg, South Africa; Lima, Peru; Karachi, Pakistan; Kampala, Uganda; Boston, MA, USA; Osaka, Sapporo, Japan; Buenos Aires, Argentina; Sofia, Bulgaria; Medellin, Columbia; Orsay, France;**

**Abstract:** To characterize the genetic determinants of resistance to antituberculosis drugs, we performed a genome –wide association study (GWAS) of 6,465 Mycobacterium tuberculosis clinical isolates from more than 30 countries.. A GWAS approach within a mixed regression framework was followed by a phylogenetics-based test for independent mutations. In addition to mutat5ions in established and recently described resistance-associated genes, novel mutations were discovered for resistance to cycloserine, ethionamide and para-aminosalicylic acid. New epistatic relationships between candidate drug-associated genes were identified. Findings also suggest the involvement of efflux pumps )drrA and Rv2688c ) in the emergence of resistance. This study will inform the design of new diagnostic tests and expedite the investigation of resistance and compensatory epistatic mechanisms.

**Comment:** We certainly need more insights into drug resistance.

<div align="right">JT</div>

**Integration of molecular typing results into tuberculosis surveillance in Germany- A –pilot study.**

**Andres et al Berlin, Stuttgart, Heidelberg, Borstel, Germany**

Abstract : An integrated molecular surveillance for tuberculosis (TB) improves the understanding of ongoing TB transmission by combining molecular typing and epidemiological data. However the implementation of an integrated molecular surveillance for TB is complex and requires thoughtful consideration of feasibility, demand, public health benefits and legal issues. We aimed to pilot the integration of molecular typing results between 2008 and 2010 in the German Federal State of Baden-Wurttemburg ( population = 10.88 million ) a preparation for a nationwide implementation Culture positive TB cases were typed by IS6110 DNA fingerprinting and results were integrated into routine notification data. Demographic and clinical characteristics of cases and clusters were described and new epidemiological links detected after integrating typing data were calculated.. Furthermore, a cross-sectional survey was performed among local public health offices to evaluate their perception and experiences. Overall, typing results were available for 83% of notified culture positive TB cases, out of which 25% were clustered.. Age < 15 years (OR =4.96, 95% CI: 1.69-14.55) and being born in Germany (OR= 2.01, 95% CI: 1.44-2.80) were associated with clustering. At cluster level, molecular typing information allowed the identification of previously unknown epidemiological links in 11 % of the clusters. In 59% of the clusters it was not possible to identify any epidemiological link. Clusters extending over fifferent counties were less likely to epidemiological links among their cases (OR=11.53, 95% CI: 3.48-98.23). The majority of local public health offices found molecular typing useful for their work. Our study illustrates the feasibility of integrating typing data into the German TB notification system and depicts its added public health value as a complementary strategy in TB surveillance,

especially to uncover transmission events among geographically separated TB patients.  It also emphasizes that special efforts are required  to strengthen the communication between local public health offices in different counties to enhance TB control.

**Comment**:  Another study to emphasise that typing must be  complimentary to direct contact action

<div align="right">JT</div>

**Molecular epidemiology of tuberculosis in Tasmania and genomic charac-terization of its first multidrug-resistant case.**

**Gautam et al; Dublin, Ireland; Hobart, Launceston, Tas., Melbourne, Vic., Australia**

**PLoS One  2018; Feb 21**

**Background:** The origin and spread of tuberculosis (TB) in Tasmania and the types of strains of Mycobacterium tuberculosis complex (MTBC) present in the population are largely unknown

**Objective:** The aim of this study was to perform the first genomic analysis of MTBC isolates from Tasmania to better understand the epidemiology of TB in the state .

**Methods:** Whole genome was applied the phylogeny of the isolates and the presence of drug-resistant mutations.  The genomic data were then cross-referenced against public health surveillance records on each of the cases.

**Results:** We determined that 83.3% of TB cases in Tasmania from 2014 -2016 occurred in non-Australian born individuals. Two possible clusters were identified based on single locus variant analysis, one from November-December 2014(n=2) with the second from May-August  2015 (n=4). We report here 5he first known isolate of multidrug-resistant  (MDR) tuberculosis in Tasmania from 2016 for which we established its drug resistant mutations and potential; overseas origin.  In addition, we characterised a case of M bovis TB in a Tasmanian-born person who presented in 2014, approximately 40 years after the first confirmed case in the states bovids.

**Conclusions:** TB in Tasmania is predominantly of overseas origin with genotypically unique drug susceptible isolates of M tuberculosis  However the state also exhibits features of TB that are observed in other jurisdictions, namely, the clustering of cases and drug resistance.  Early detection of TB and contact tracing , particularly of overseas-born cases, coordinated with rapid laboratory drug-susceptibilty testing and molecular typing , will be
essential for Tasmania to reach the World   Health Organisation TB eradication goals for low-incidence countries.

**Comment:** It is good to have goals, but I haven't seen WHO goals for TB met yet and doubtful if they ever will.

<div align="right">JT</div>

# Children

**Congenital tuberculosis presenting as otorrhoea in a preterm infant**

**Aldana-Aguirra et al        Edmonton, Calgary, Canada**

**BMJ Case Rep   2018; Jan 17**

**Abstract:** a premature infant of 25 weeks gestational age presented at 8 weeks after birth with otorrhoea from the left ear.  Following a course of topical and systemic antibiotics, the patient deteriorated developing facial nerve paralysis and cervical lymphadenitis. Contrast –enhanced CT and MRI of the head showed a destructive process of the left temporal bone.  These findings prompted the clinicians to send swabs from the purulent discharge from the ear for acid-fast bacilli stain.  Furthermore surgical exploration and debridement were undertaken.  Cultures from the ear discharge and biopsy taken from during the surgical revealed the presence of Mycobacterium tuberculosis complex. The patient developed necrotizing otitis media , left temporal bone osteomyelitis and cervical lymphadenitis.  The infant's mother was found to have an endometrial biopsy positive for M. tuberculosis suggesting the diagnosis of congenital tuberculosis,
**Comment:** It has long been an aphorism that if the diagnosis is in doubt, always look for tuberculosis.

<div align="right">JT</div>

**The influence of BCG on vaccine reponses: a systematic review.**

**Zimmermann et al      Melbourne, Vic., Australia;  Basel, Switzerland**

**Expert Rev Vaccines  2018; June 8**

**Introduction:** Bacillus Calmette-Guerin (BCG) vaccine is one of the most widely used vaccines worldwide.  In addition to providing protection against tuberculosis, it has non-specific (heterologous) immunomodulatory effects.

**Areas Covered:** In our systematic review, we found eight studies, involving 2439 participants, investigating the influence of BCG vaccination on the humoral response to 16 different vaccines. A beneficial effect of BCG on vaccine responses was reported on five of the eight studies. Previous or concurrent administration of BCG was associated with significantly higher levels of antibodies against hepatitis B, polio virus type 1, pneumococcus and influenza in some studies. No study reported a statistically significant in the response to other vaccines, though in many cases higher antibody levels were observed in the BCG-vaccinated group. One study reported lower levels of antibodies against hepatitis B in BCG vaccinated participants.

**Expert Commentary:** The studies in this review suggest that BCG modulates immune responses to other vaccines. Future studies should focus on the influence of BCG vaccine strain and the optimal timing of administration to exploit the immunomodulatory effects of BCG to improve vaccine efficacy and duration of protection .

**Comment:** These findings fit nicely with population studies which show that BCG vaccinated infants and young children have a lower mortality rate from non tuberculosis disease than those not vaccinated. In addition experiment scientists have long known that Freund's adjuvant can be used on experimental animals to stimulate the immune response.

JT

# Risk Factors

# Intensity of exposure to pulmonary tuberculosis determines the risk of tuberculosis infection and disease.

## Acun-Villaorduna et al Boston, MA, Newark, NJ, USA; Vitoria, Brazil

## Eur Respir J 2018; Jan 18

**Abstract:** Household contacts of pulmonary tuberculosis (TB) patients are at increased risk of TB infection and disease. However, their risk in relation to the intensity of exposure remains unknown.. We studied smear-positive cases and their household contacts in Vitoria, Brazil. We collected clinical, demographic and radiographic information from TB cases and obtained tuberculin skin test (TST) and QuantiFERON-TB-Gold (QFT) results from household contacts. We measured intensity of exposure using a proximity score and sleep location in relation to the TB index case and defined infection by TST>/== 10 mm or QFT >/=0.35 UI ml-1. We ascertained secondary TB cases by reviewing local and statewide case registries. We included 160 TB index cases and 894 household contacts. 464 had TB infection and 23 (2.6%) developed TB disease. Risk of TB TB infection and disease increased with more intense exposures. In an adjusted analysis, the proximity score was associated with TB disease (OR 1.61, 95% CI 1.25-2.08; p< 0.0001); however, its diagnostic performance was only of moderate intensity among household contacts. Moreover, its its diagnostic performance was still suboptimal. A biomarker to target preventive therapy is urgently needed in this at-risk population.

**Comment:** intensity of contact may also relate to size and quality of housing and hence poverty.

JT

# Non-tuberculous mycobacteria

## Non-tuberculous mycobacteria in milk from positive cows in the intradermal comparative cervical tuberculin test: implications for human tuberculosis infections.

## Bolanos et al Sao Paulo, Goias, Brazil; Narino, Columbia

## Rev Inst Med Trop Sao Paulo 2018; 60:e6

**Abstract:** Although the tuberculin test represents the main in vivo diagnostic method used in the control and eradication of bovine tuberculosis, few studies have focused on the identification of of mycobacteria in the milk from cows positive to the tuberculin test. The aim of this study was to identify Mycobacterium species in milk samples from cows positive to the comparative intradermal test. Milk samples from 142 cows positive to the comparative intradermal test carried out in 4766 were aseptically collected, cultivated on Lowenstein-Jensen and Stonebrook media and incubated for up to 90 days. Colonies compatible with mycobacteria were stained by Ziehl- Neelsen to detect acid-fast bacilli, while to confirm the Mycobacterium species, conventional PCR was performed. Fourteen mycobacterial strains were isolated from 12 cows (8,4%). The hsp65 gene sequencing identified M. engbaekii (N=5}. M. arupense (n=4), M. nonchromogenicum (n=3} and M heraklionense (n=2) species belong to the Myobacterium terrae complex. Despite the absence of M tuberculosis complex species in the milk samples, identification

of these mycobacteria, highlights the risk of pathogen transmission from bovines to humans throughout milk or dairy products, since many of t5he mycobacterial species described here have been reported in pulmonary and extra pulmonary diseases both in immunocompetent and immunocompromised people.

**Comment:** In countries where bovine TB has been eliminated but a cow shows a positive TST should we culture the milk or just destroy the cow?

<div align="right">JT</div>

# Multidrug-resistance

## Multidrug-resistant tuberculosis in Queensland, Australia: an ongoing cross-border challenge.

## Baird et al Brisbane, Cairns, Queensland ,Australia.

### Int J Lung Dis 2018; 22:206

**Setting:** Multidrug-resistant tuberculosis (MDR-TB) is a growing concern worldwide. In Australia, although the incidence of MDR-TB remains low Queensland is at increased risk due to its proximity to Papua New Guinea (PNG).

**Objectives:** To explain the epidemiology, clinical features and outcome of MDR-TB in Queensland, with comparison between cross-border PNG and non-cross-border patients:

**Design:** Retrospective case series of all MDR-TB patients in Queensland between 1 January 200- 31 December 2014.

**Results:** Ninety six patients were diagnosed with MDR-TB in Queensland between 2000 and 2014. The majority were cross-border PNG nationals diagnosed within the Torres Strait (n=73, 76%) cross –border patients were younger (27,4 vs 36.3 years, P=0.02) had spent less time in Australia before diagnosis (< 1 vs 19 months, P<0.01), had molecular surveillance for TB, higher rates of smear positivity (67.1% vs 40%, P<0.04 and were less likely to have received a second line injectable agent (54. 5.% vs71.4%, P =0,05). Cross-border patients had significantly lower rates of treatment success than non-cross-border patients (47.9 % vs 85.7%,P<0.01).

**Conclusion:** MDR-TB cases in Queensland are largely a result of cross-border PNG nationals, with poorer outcomes seen in this cohort. Continued strengthening of the regions TB program, with a focus on cross –border patients, is required.

**Comment:** Whether the initiative of treating such patients on Daru island in PNG rather than in the Torres Straits Islands is successful has yet to be seen.

## Pulmonary resection in the treatment of multidrug-resistant tuberculosis: a case series

## Wang et al Shanghai, Suzhou, Zhengzhou, Hefei, China

### Medicine (Baltimore) 2017;Dec;96(50)

**Abstract:** Multidrug-resistant (MDR) and extensive drug-resistant (XDR) tuberculosis (TB) are significant health problems throughout the world. Although the main treatment is medical, adjunctive surgical resection may increase the chance3 of cure in selected patients with MDR-TB and XDR-TB.. This case aimed to pr4esent a case series of patients who underwent surgical resection for MDR-TB between March 2008 and November 2011. Surgical resection was performed on 54 patients including 34 with MDR-TB and 20 with XDR-TB at the Departments of surgery of Shanghai Public Health Clinical Center Shanghai), Henan Chest Hospital (Henan), and Anhui Chest Hospital (Henan). Preoperative sputum smear samples were positive for 28 patients and sputum quantitative polymerase chain reaction was positive for 32. Patients were treated according to a standard tr4eatment protocol for a mean of 4.2 months be3fore the operation. The variables that affected treatment outcomes wee identified through multivariate regression analysis. Fifty four patients operated for MDR-TB with localized disease usually complicated by cavity formation or destroyed lung. Thirty seven were males and 17 were females. Median age was 37.8 (range 20-75 years). Lobectomy was performed in 46 patients and pneumonectomy in 8. Muscle flaps were used in 36 of the patients with lobectomy and 8 with pne3umonctomy. Various complications o9ccure in 6 (11.1%) patients bronchopleural fistula in 1 patient, bleeding in 2 patients and prolonged air leak in 2 patients. A favourable outcome was achieved in 47 patients (87%)who underwent surgical resection. Higher body mass index was associated with better outcome( odds ratio =0.537, 95% CI 0.310-0.928, P=. 026). Patients with MDR –TB had good treatment outcomes after adjunctive pulmonary resection , and with fewer complications. Higher BMI was related to a favorable outcome.

**Comment** A mean period of chemotherapy of just over 4 months before surgery seems rather short . It would be nice to know what proportion of MDR-TB and XDR-TB patients were selected for surgery.

**Cost analysis of rapid diagnostics for drug-resistant tuberculosis.**

**Groessi et al  San Diego. CA, Little Rock, AR, USA; Cape Town, South Africa; Mumbai, India; Chisinau, Moldova**

**Background:** Growth-based drug susceptibility (DST) is the reference standard for diagnosing drug-resistance tuberculosis (TB), but standard time to result   (TTR) is typically =/>3 weeks.  Rapid tests can reduce that TTR to days or hours, but accuracy may be lowered.  In addition to the TTR and test accuracy, the cost of a diagnostic test may affect whether it is adopted in   clinical circles.  We examine the cost-effectiveness of rapid diagnostics for extremely drug resistant  (XDR-TB ) in in three different high-prevalent settings.

**Methods:** 1128 patients with confirmed TB were enrolled at clinics in Mumbai, India, Chisinau, Moldova and Port Elizabeth, South Africa. Patient sputum samples underwent DST for first and second line  TB  drugs  using  2  growth-  based (MGIT,MODS) and molecular (Pyrosequencing [ PSQ] , line probe assays [LPA] .  TTR was the primary measure of effectiveness. Sensitivity and specificity were also evaluated.  The cost to perform each test at each site was recorded and included test-specific materials, personnel and equipment costs. Incremental   cost-effectiveness   ratios   were calculated in terms of $/day saved.   Sensitivity analyses examine the impact of batch size, equipment  and personnel costs.

**Results**: our prior results indicated that the LPA and PSQ returned results in a little over 1 day.  Mean cost per sample without equipment or overhead was %23, $28, $33 and $41 for the MODS, MGIT, PSQ and LPA, respectively.  For diagnosing XDR-TB, MODS was the most accurate, followed by PSQ and LPA.   MODS  was  quicker  and  less  costly  than MGIT.  PSQ and LPA were considerably faster but cost more than MODS, Batch size and personnel costs were the main drivers of cost variation.

**Conclusions:** Multiple factors must be weighed when selecting a tests for diagnosis of XDR-TB. Rapid tests can greatly improve the time required to diagnose drug-resistant TB, potentially improving treatment  success  and  preventing  the  spread  of XDR-TB.  Faster time to result must be weighed
 against against the potential for reduced accuracy and increased costs/

**Comment:** so a lot depends on how often one needs to test for XDR-TB   and how much laboratory staff are paid.

                                             JT

# Surgery

**Surgical   aspects   of   pulmonary tuberculosis : an update.**

**Dewan  et  al       New  Delhi,  India; Worcestor, MA, USA**

**Abstract:** Tuberculosis remains a major global medical  challenge  and  concern.    In  the  world's population of over 7.4 billion people, 8.6 million are estimated  to  be  infected  with  Mycobacterium tuberculosis;    another  2.3  billion  have  latent tuberculosis.  There is an annual incidence of 16000 new cases in the USA and 7-8 million new cases world  wide,  of  which  440,000  are  multidrug-resistant or extensively drug-resistant, mainly in developing  countries  or  emerging  economies. According to the World Health Organisation , the incidence of tuberculosi8s is 133 cases 100,000 of the population;  3.3% new cases are drug resistant and 20% are already treated cases.  Of the drug-resistant cases, 9.7 % are extensively drug-resistant. The  annual  global  mortality  attributable  to tuberculosis is over 1.3  million people.  The association with HIV/AIDS in 430,00 people has compounded the the global concern and challenge. This review presents the historical indications for surgical treatment of tuberculosis, reviews the current literature and clinical experience, land collates  this  into  increased  awareness  and contemporary understanding of the indications and need  for  surgery  in  primary  active  tuberculosis, adjuvant surgical treatment for multidrug-resistant tuberculosis,  and  the  complications  of  chronic tuberculosis  sequelae  or  previous  tuberculosis surgery.

**Comment:** The authors use the term "primary tuberculosis" in a different sense to what your editor understands

                                             JT

# Extra pulmonary tuberculosis

**First   case   of   sexual   transmitted asymptomatic     female     genital tuberculosis from spousal epididymal tuberculosis   diagnosed   by   active screening.**

**Kimura  et al  Tokyo, Japan**

**Abstract:** Tuberculosis screening was performed for a healthy asymptomatic woman to determine whether she had been infected with active genital tuberculosis via sexual intercourse with her husband who had epididymal tuberculosis. Vaginal swab culture yielded Mycobacterium tuberculosis. Furthermore, whole genome sequencing revealed that the two causative isolates were genetically identical. To the best of our knowledge, this is the first report of sexual transmission of genital tuberculosis from a man to an asymptomatic woman detected by active screening for genital tuberculosis and molecular analysis, including whole-genome-sequencing. Active screening for genital tuberculosis in the female partner should be considered soon after diagnosis of male genital tuberculosis even when the female partner is asymptomatic.

**Comment:** Curettage of the endometrium might have provided evidence to determine what treatment regimen was indicated.

JT

## Spinal tuberculosis

**Dunn et al Cape Town, South Africa**

**Abstract:** Tuberculosis (TB) remains endemic in many parts of the developing world and is increasingly in the developed world due to migration. A total of 1.3 million people die annually from the disease. Spinal TB is the most common musculoskeletal manifestation , affecting 1 to 2 % of all cases of TB.. The coexistence of HIV, which is endemic in some regions, adds to the burden and the complexity of management. This review discusses the epidemiology , clinical presentation , impact of HIV and both the medical and surgical options in the management of spinal TB.

**Comment:** With present day imaging the diagnosis should be made early enough before the patient requires surgery for deformity.

JT

# Treatment

## Liver toxicity associated with tuberculosis chemotherapy in the REMMox study/

**Tweed et al London, St Andrews, UK; Cape Town, Brits, Johannesburg, South Africa; San Francisco, CA, USA; Melbourne . Vic, Australia .**

**Background:** Drug-induced liver injury (DILI) is a common complication of tuberculosis treatment. We utilized data from the REMoxTB clinical trial to describe the incidence of predisposing factors and the natural history in patients with lover enzymes levels elevated in response to tuberculosis treatment..

**Methods:** Patients received either standard tuberculosis treatment (2 EHRZ.4HR), or or a 4 month regimen in which moxifloxacin replaced either ethambutol (isoniazid arm, 2 MHRZ/2 MHR) or isoniazid (ethambutol arm, ( 2 EMRZ/2 MR). hepatic enzymes were measured at 0, 2, 4, 8, 12 and 17 weeks and as clinically indicated during reported adverse events. Patients included were those receiving at least one dose of drug and withy two or more hepatic enzyme measurements.

**Results:** A total of 11928 patients were included (639 2EHRZ/4 RH, 654 2 MHRZ/2MHR and 635 2 EMRZ/2 MR)/. DILI was defined as peak alanine (aminotransferase (ALT) $>/=$ 5 times the upper limit of normal (5xULN) or ALT $>/=$3x ULN with total bilirubin :$>$ 2xULN. DILI was identified in 58 of the 1928 (3%) patients at a medium time of 28 days (interquartile range IQR 14.56. ) Of 639 patients taking standard tuberculosis therapy, 41 experienced clinically significant enzyme levels (peak ALT $>/=$ 3xULN On standard therapy , 21.1% of patients aged $>$55 years developed a peak ALT/aspartate aminotransferase (AST) $>/=$3x ULN (p=0.01) and 25% of HIV-positive patients experienced a peak ALT/AST $>/=$ 3 x ULN compared to 9% 0f HIV negative patients (p=0.160) The median peak ALT/AST was higher in isoniazid containing arms vs moxifloxacin arms (p<0.05) and lower min moxifloxacin –containing arms vs no-moxifloxacin arms (p<0.05). Patients receiving isoniazid reached a peak ALT $>$/9.5 days earlier than those on the ethambutol arm (median time of 28 days vs 18,5 days). Of the 67 Asian patients with a peak ALT.AZST $>/=$ 3 x ULN, 57 (85.1%) were om an isoniazid –containing regimen (p=0.008).

**Conclusions:** Our results provide evidence of the risk of DILI in tuberculosis patients on standard treatment. Older patients on standard therapy, HIV –positive patients, Asian patients and those receiving isoniazid were at higher risk of elevate\ted enzyme levels. Monitoring hepatic enzymes during the first 2 months of standard therapy detected approximately 75% of patients with a peak enzyme elevation $>/=$ 3x ULN ,suggesting this should be the standard of care. These results provide evidence for the potential of moxifloxacin in hepatic sparing.

**Comment:** No surprises here although an elevation of ALT at 3 times normal sometimes reverses its without drug suspension.

<div align="right">JT</div>

# Diagnosis

## Efficacy of fine-needle aspiration cytology in the diagnosis of tuberculous cervical lymphadenitis.
**Rammeh et al  Tunis, Tunisia**

**Acta Cytol  2018;62:99**

**Objective:** This study assesses the role of fine-needle aspiration cytology (FNAC) in the diagnosis of tuberculous lymphadenitis (TL) in comparison with histology and bacteriology findings.
**Study design:** We undertook a descriptive retrospective study of 937 FNAC specimens from 851 patients  with (enlarged-Ed.) cervical lymph nodes.  The FNAC findings were then compared to histopathology  and bacteriology.
**Results:** Of the 937 aspirates, the cytopathological diagnoses consisted of of 426 (55.9%) TL,185 (24,3%) reactive lymphoid hyperplasia, 18 (2,3%) suppurative inflammation, 78 )10.2%) malignant metastatic tumour and 54 (7%) lymphoma.  Of the 426  TL cases , 171  were diagnosed by FNAC combined with bacteriological examination.  In this group , 22 cases were found to be positive on Ziehl-Neelsen stain and 16 by culture.  A histopathology report was available for 62 cases.  Compared to histopathology , the overall diagnostic sensitivity, specificity , positive predictive ability (PPV) and negative predictive ability (NPV)  of NPAC in the diagnosis of TL were respectively , 96.77, 100,100 and 96.67%.  When comparing bacteriology to histopathology, these values were 97.44, 100, 100, and 91.67 %
**Conclusion:** Our study shows that FNAC is a sensitive and specific test for the diagnosis of cervical TL.
**Comment:** Convincing.

<div align="right">JT</div>

# Social and political issues

## The impact of social protection and poverty elimination on global tuberculosis incidence: a statistical modelling analysis of sustainable development goal 1

**Carter et al    London, UK; Geneva, Switzerland; Stockholm, Sweden**

**Lancet Glob Health  21018 May;6: e 514**

**Background:** The End TB Strategy and the Sustainable Developments Goals (SDGs) are intimately linked by their common targets and approaches.  SDF1 aims to end extreme poverty and expand social protection by 2030.  Achievement of SDG 1 is likely to affect the tuberculosis epidemic through a range of pathways.  We estimate the reduction in global tuberculosis incidence that could be obtained by reaching SDG1.
**Methods:** We developed a conceptual framework linking key indicators od SDG1 progress to tuberculosis incidence via well described risk factor pathways and populated it with data from the SDG data repository and the WHO tuberculosis database for 192 countries.  Correlations and mediation analyses informed the strength of the association between the SDG1 subtargets and tuberculosis incidence, resulting in a simplified framework for modelling.  The simplified framework  linked key indicators  for SDG1 directly to tuberculosis incidence.  We applied an exponential decay model based on linear associations between SDG1 indicators and tuberculosis incidence to estimate tuberculosis incidence in 2035.
**Findings:** Ending extreme poverty resulted in a reduction in global incidence of tuberculosis of 33.4 % (95 % credible interval 15.5- 44.5) by 2035 and expanding social protection coverage resulted in a reduction in incidence of 76.1%( 45.2-89.9) by 2035, both pathways together resulted in a reduction in incidence of 84.3% (54.7- 94.9)_
**Interpretation:** Full achievement of SDG1 could have a substantial effect on the global burden of tuberculosis.  Cross-sectional approaches that promote poverty reduction and social protection expansion will be crucial complements to health interventions, accelerating progress progress towards the End TB targets.
**Comment:** We have known for a long time that as poverty grew less in western Europe, the US and Australasia, that mortality from tuberculosis fell.

<div align="right">JT</div>

# Extensive drug-resistant-tuberculosis

## Mortality and associated factors of patients with extensive drug-resistant tuberculosis: an emerging  public health crisis in China.

**Bei et al    Changsha, Hengyang, and Chenzhou    Hunan, Beijing, Wuhan, Hubei, China**

## BMC Infect Dis   2018 ; 18: 261

**Background:** Limited treatment options of extensive drug-resistant tuberculosis (XDR-TB) have led to high mortality worldwide. Relevant data about mortality of XDR-TB patients in literature are limited and likely underestimate the real situation in China, since the the majority of patients are lost to follow-up after discharge from TB hospitals. In this study, we sought to investigate the mortality and associated risk factors of human immunodeficiency virus (HIV)-negative patients with XDR-TB in China.

**Methods**: All patients who were diagnosed with XDR-TB for the first time in four TB care centers across China between March 2013 and February 2015 were consecutively enrolled. Active tracking through contacting patients or family members by phone or home visit was conducted to obtain patients' survival information by February 2017. Multivariate Cox regression models were used to evaluate factors associated with mortality.

**Results:** Among 67 patients enrolled, the mean age was 48.7 (SD)=16.7, and 51 (76%) were men. Fourteen patients were treatment naïve at diagnosis indicating primary transmission . During a median follow-up period of 32 months, 20 deaths occur, with an overall mortality of 128 per 1000. Among patients who were dead , the median survival was 5.4 months (interquartile range (IQR); 2,2 -17.8. Seventeen (85%) of them died at home, among whom the median interval from discharge to death was 8.4 months (IQR: 2.0-18.2). In Cox proportional hazard regression models, body mass index (BMI) < 18.5 Kg/M2 (adjusted hazard ratio (aHR) =4.9 (95%CI 1.7-13.2.) , or a clinically significant comorbidity , including heart ,lung liver or renal disorders or auto-immune diseases (aHR= 3.5, 95% CI 1.3-9.4 were factors independently associated with increased mortality.

**Conclusion**: Our study suggested an alarming situation of XDR-TB patients in China with a sizable proportion of newly transmitted cases, a high mortality, and a long period in community . This observation calls for actions to improve XDR-TB case management in China, including regimens with high chances of cure and palliative care m and enhanced infection control measures.

Comment: Although the follow-up period was short , the mortality trend seems like a return to pre-chemotherapy days.  No doubt possession of a Beijing strain might worsen the prognosis.

JT

## Zoonoses

## Prevalence of bovine tuberculosis in India: a systematic review and meta-analysis.

**Srinivasan et al    Pennsylvania, USA; Cambridge, UK**

**Abstract:** Bovine tuberculosis (bTB) is a chronic disease of cattle that impacts productivity and represents a major health threat.  Despite the considerable economic costs and zoonotic risk consequences associated with the disease, accurate estimates of bTB prevalence are lacking in many countries, including India, where national control programmes are not yet implemented and the disease is considered endemic.  To address this critical knowledge gap , we performed a systematic review of the literature and a meta-analysis to estimate bTB prevalence in cattle in India and provide a foundation for the future formulation of rational disease control strategies and the accurate assessment of economic and health Impact risks. The literature search was performed in accordance with PRISMA guidelines and identified 285 cross-sectional studies on bTB in cattle in India across four electronic databases and handpicked publications. Of these, 44 articles were included, contributing a total 82,419 cows and buffaloes across 18 states ands one union territory in India.  Based on a random-effects (RE) meta-regression ,model, the analysis revealed a pooled prevalence estimate of 7.3 % (95% CI, 5.6-9.5), indicating that there may be an estimated 21.8 million (95% CI, 16.6-28.4) infected cattle in India- a proportion greater than the total number of dairy cows in the United States. The analyses further suggest that production system, species, breed, study location , diagnostic technique, sample size and study period are likely moderators of bTB prevalence in India and need to be considered when developing future disease surveillance and control programmes.  Taken together with the projected increase in intensification of dairy production  and the subsequent increase in the likelihood of zoonotic transmission , the results of our study suggest that attempts to eliminate tuberculosis from humans will require simultaneous consideration of, bTB control in cattle populations in countries such as India.

Comment: A reminder that when travelling in India, milk in your sweet tea from a roadside tea house might not be as safe as you think.

JT