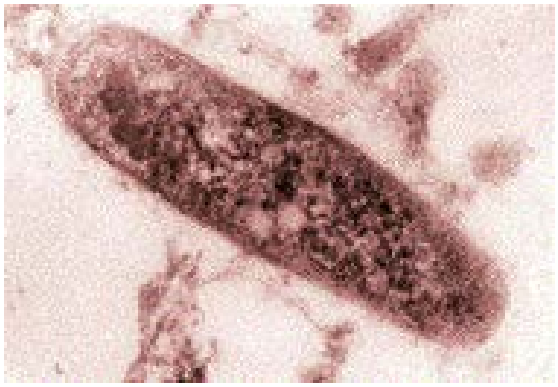
The Australian Tuberculosis Review

February 2015

All Australasian Edition

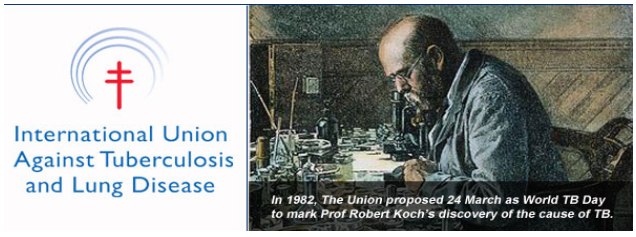


M. tuberculosis EM Photo

Forthcoming Meetings

5th Asia-Pacific Region Conference of the International against Tuberculosis and Lung Disease Sydney . 31 August-2 September 2015 www.thearc.org.au

46 th Union World Conference on Lung Health Cape Town South Africa 2-6 December 2015



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Contents

Editorial: In this edition we are celebrating that for the first time in the history of this periodical, all the articles cited are written by at least one author working from Australasian institutions. For many years the editors were unable to find more than two or three published papers on human TB from Australasia for each edition. This has changed dramatically in the last few years, so that by the end of 2014, it is possible to include only publications from Australasia. The reasons for this proliferation would not seem to be the lack of control of TB in Australia and New Zealand, even though the rate is creeping up in Australia.. There has been a proliferation of research institutes in Australia, particularly in Sydney, Melbourne and Darwin and they have become particularly active in tuberculosis research. But why choose to research a disease that is rare in our countries?

Across the world health researchers are looking outside their wealthy countries for projects and what better than to target those three diseases that are receiving so much attention and money - tuberculosis, malaria and HIV/AIDS. Foreign graduates are being attracted to the high standards of Australasian graduate schools. What better topic for a PHD for a graduate from a TB ridden country than aspects of that disease. By collaboration with the institutions of their home countries, adequate source material can be gathered then analysed in an institution in Australia. This is a most encouraging trend, but we hope the Review will still have room to allow us to present groundbreaking studies from outside Australasia when they appear in the literature.

News from Australia

Tuberculosis Notifications in Australia, 2011.

Bareja et al National Tuberculosis Advisory Committee

Commun Dis Intell 2014; 38: E 356

Abstract: The National Notifiable Diseases Surveillance system received 1,385 tuberculosis (TB) notifications in 2011,representing a rate of 6.2 cases per 100,000 population. While Australia has maintained a rate of 5 to 6 cases per 100,000 for TB since the mid-1980s, there has been a steady increase in incidence over the past decade. In 2011, Australia's overseas –born population continued to represent the majority of TB notifications (88%) with a notification rate of 20.2 per 100,000. The incidence of TB in the Australian-born Indigenous population has fluctuated over the last decade and showed no clear trend; however, in 2011 the notification rate was 4.9 per 100,000, which is a notable decrease from the 7.5 per 100,000 recorded in 2010. The incidence of TB in the Australian-born non-indigenous population has continued to remain low at 0.9 per 100,000. Australia continued to record only a small number of multidrug-resistant TB (MDR-TB) cases nationally (n=25), all of which were identified in the overseas born population. To ensure that Australia can retain its low TB rate and work towards reducing rates further, it is essential that Australia maintains good centralized national TB reporting to monitor trends and identify at-risk populations and work towards reducing rates further, and continues to contribute to global TB initiative.
Comment: Good national TB reporting requires adequate staff and adequate staff requires government expenditure at both State, Territory and Commonwealth levels. Is this the explanation for the delay in producing national data?

JT

Tuberculosis in Australia: bacterio-logically-confirmed cases and drug resistance, 2011: a report of the Australian Mycobacterium Reference Laboratory Network.

Lumb et al AMRLN, Adelaide, Melbourne, Sydney, Brisbane, Perth.

Commun Dis Intell 2014; 38: E369

Abstract: The Australian Mycobacterium Reference Laboratory Network collects and analyses laboratory data on new cases of disease caused by the Mycobacteria tuberculosis complex. In 2011, a total of 1057 cases were identified bacteriologically; an annual reporting rate of 4.6 cases 100,000 population. Eighteen children aged less than 15 years plus an additional 11 children from the Torres Strait Protected Zone had bacteriologically-confirmed tuberculosis. Results of in vitro drug susceptibility testing were available for 1056 isolates for isoniazid, rifampicin, ethambutol and pyrazinamide. A total of 107 (10.0%) isolates of M. tuberculosis were resistant to at least one of these anti-tuberculosis agents. Resistance to at least isoniazid and rifampicin (defined as multidrug-resistance, MDR) was detected in 25 (2.4%) isolates; 18 were from the respiratory tract (sputum n=14. bronchoscopy n=3, tissue n=1). Ten (55.6%) of the MDR-TB-positive sputum specimens were smear positive, as was a single sample from a lymph node. Ten patients with MDR-TB were Papua New Guinea (PNG) nationals from the Torres Strait protected zone. If these PNG nationals are excluded from the analysis, the underlying MDR-TB rate in Australia was 1.4%. No cases of extensively drug-resistant TB (defined as MDR-TB with additional resistance to a fluoroquinolone and an injectable agent) were detected in 2011.
Comment: Let us hope that Commonwealth initiative to control TB in the Western Province of Papua New Guinea by providing staff and facilities at Daru island will see the number of MDR-TB cases arriving in the Torres Straits Protected Area decrease in 2012-2015. Without a back up in the Northern Torres Straits Islands, this hope may not be fulfilled.

JT

Treatment and Prognosis

An update on the use of rifapentine for tuberculosis therapy.

Chan et al Sydney NSW Australia

Expert Opin Drug Deliv 2014; 11: 421

Introduction: Tuberculosis (TB) remains rampant throughout the world, in large part due to the lengthy treatment times of current therapeutic options. Rifapentine, a rifamycin antibiotic, is currently approved for intermittent dosing in the treatment of TB. Recent animal studies have shown that more frequent administration of rifapentine could shorten treatment times for both latent and active TB infection. However, these results were not replicated in a subsequent human clinical trial.
Areas Covered: This review analysis the evidence for more frequent administration of rifapentine and the reasons for the apparent lack of efficacy in shortening treatment times in human patients. Inhaled delivery is discussed as a potential option to achieve the therapeutic effect of rifapentine by overcoming the barriers associated with the oral administration of this drug. Avenues for developing an inhalable form of rifapentine are also presented.
Expert Opinion: Rifapentine is a promising active pharmaceutical ingredient with potential to accelerate treatment of TB if delivered by inhaled administration. Progression of fundamental work on

inhaled anti-tubercular therapies to human clinical trials is essential for determining their role in future treatment regimens. While the ultimate goal for global TB control is a vaccine, a short and effective treatment option is equally crucial.
Comment: And safe as well.

JT

High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena.

Ralph et al Darwin NT Australia

PloS One 2013; 8: e80302

Background: In pulmonary tuberculosis (PTB), morbidity during treatment and residual pulmonary disability can be underestimated.
Methods: Among adults with smear-positive PTB at an outpatient clinic in Papua, Indonesia, we assessed morbidity at baseline and during treatment, and 6-month residual disability, by measuring functional capacity (six minute walk test [6MWT] and pulmonary function), quality of life (St George's Respiratory Questionnaire [SGRQ] and Adverse Events [AE] : new symptoms not present at outset). Results were compared with findings in locally-recruited volunteers.
Results: 200 PTB patients and 40 volunteers were enrolled, 6MWT was 497m (interquartile range 460-529) in controls versus 408m (IQR 346-450) for PTB patients at baseline (p<0.0001) and 470 [IQR 418-515] in PTB patients after 6 months (p=0,02 versus controls). SGRQ total score was 0 units (IQR 0-2.9) in controls, versus 36.9 (27.4-52.8) in PTB patients at baseline (P<0.0001) and 4.3 (1.7-8.8) by 6 months (P<0.0001). Mean percentage of predicted FEV1 was 92% (SD 19.9) in controls, versus 93% (19.4) in PTB patients at baseline (P<0.0001) and 71% (17.5) by 6 months (P<0.0001). After 6 months, 27% of TB patients still had at least moderate to severe pulmonary function impairment, and 57% still had respiratory symptoms, despite most achieving "successful" treatment outcomes, and reporting good quality of life. More advanced disease at baseline (longer illness duration, worse baseline X-ray) and HIV positivity predicted residual disability. AE at any time during treatment were common: itch 59%, arthralgia 58%, headache 40%, nausea 33%, vomiting 16%.
Conclusion: We found high 6-month residual pulmonary disability and high AE rates. Although PTB treatment is highly successful, the extent of morbidity during treatment and residual impairment could be overlooked if not specifically sought. Calculations of PTB-related burden of disease should acknowledge that TB-related morbidity does not stop at 6 months. Early case detection and treatment are key in minimizing residual impairment.
Comment: A useful reminder that far advanced PTB could and did leave those affected with both obstructive and restrictive defects, before the decline in such categories of TB began in Australia some 40 years ago.

JT

Survival and predictors of death after successful treatment among smear positive tuberculosis: a cohort study.

Moosaszadeh et al Kerman and Teheran, Iran; Melbourne, Vic., Australia

Int J Prev Med 2014; 8: 1005

Background: Tuberculosis (TB) can affect the patients' life even after successful treatment. In this study, we aimed to determine the survival rate of patients with smear positive TB after successful treatment and identify the predictors of mortality.
Methods: This was a prospective study. The source of data was the TB registry system in Iran and 964 patients were eligible for the study. The life table was used to determine the annual survival rate. Survival curves were estimated using Kaplan-Meier and were compared using the log-rank test. In order to determine the predictors of survival, four models of Cox regression , exponential, Weibull and log-logistic fitted and finally exponential model with minimum akaike information criteria and Bayesian information criterion values were selected. Then, variables with significant levels <0.2 in univariate analysis were entered into the multivariate model. Hazard ratios with a confidence interval of 95% were used to measure the association.
Results: A total of 149 patients (15.5%) died during the follow-up period. The median of survival time after successful treatment was 10.5 years and survival probability for 11 years after successful treatment was 70%. Furthermore, previous TB treatment, high age, suffering from kidney failure and cancer were predictors of mortality after successful treatment.
Conclusions: This study showed that smear positive pulmonary tuberculosis even after successful treatment has an adverse effect on the patient's survival and leads to a decrease in their survival rate in the long run. Furthermore, individuals with a history of previous TB treatment had much lower survival rates.
Comment: There was an excess of diabetics in this study and one assumes this is the reason why chronic renal failure was such an important cause of death. It is a pity that patients weren't graded according to socio-economic status.

JT

Population Studies

Global, regional and national incidence and mortality for HIV, tuberculosis and

malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.

Murray et al Melbourne, Vic., Sydney NSW, Brisbane, Qld., Australia and 50 other countries.

Lancet 2014;384:1005

Background: The Millennium Declaration in 200 brought special global attention to HIV, **tuberculosis** and malaria through the formation of Millennium Development Goal (MDG)6. The Global Burden of Disease 2013 study provides a consistent and comprehensive approach to disease estimation for between 1990 and 2013, and an opportunity to assess whether accelerated progress has occurred since the Millennium Declaration.
Methods: To estimate incidence and mortality for HIV, we used the UNAIDS Spectrum model appropriately modified based on a systematic review of available studies of mortality with and without antiretroviral therapy (ART). For concentrated epidemics, we calibrated spectrum models to fit vital registration data corrected for misclassification of HIV deaths. In generalized epidemics, we minimized a loss function to select epidemic curves most consistent with prevalence data and demographic data for all cause mortality. We analysed counterfactual scenarios for HIV to assess years of life saved through prevention of mother-to-child transmission (PMTCT) and ART**. For tuberculosis, we analysed vital registration and verbal autopsy data to estimate mortality using cause of death ensemble modeling. We analysed data for corrected case-notifications, expert opinions on the case detection rate, prevalence surveys and estimated cause-specific mortality using Bayesian meta-regression to generate consistent trends in all parameters.** We analysed malaria mortality and incidence using an updated cause of death database, a systematic analysis of verbal autopsy validation studies for malaria, and recent studies (2010-13) of incidence, drug resistance, and coverage of insecticide-treated bed nets.
Findings: Globally in 2013, there were 1.8 million new HIV infections (95% uncertainty interval 1.7 million to 2.1million), 29.2 prevalent HIV cases (28.1 to 31.7) and 1.3 million HIV deaths (1.3 to 1.5). At the peak of the epidemic in 2005, HIV caused 1.7 million deaths (1.6 to 1.9). Concentrated epidemics in Latin America and eastern Europe are substantially smaller than previously estimated. Through interventions including PMTCT and ART, 19.1 million life- years (16.6million to 21.5 million) have been saved 70.3 % (65.4 to 76.1) in developing countries. From 2000 to 2011, the ratio of development assistance for health for HIV to years of life saved through intervention was US 4498 in developing countries. **Including in HIV-positive individuals, all-form tuberculosis incidence was 7.5 million (7.4 to 7.7), prevalence was 11.9 million (11.6 to 12.2) and number of deaths was 1.4 million (1.3 to 1.5) in 2013. In the same year and in only individuals who were HIV-negative, all-form tuberculosis incidence was 7.1 million (6.9 to 7.3), prevalence was 11.2 million (10.8 to 11.6), and number of deaths was 1.3 million (1.2 to 1.4). Annualised rates of change for incidence, prevalence and death became negative after 2000. Tuberculosis in HIV-negative individuals disproportionately occurs in men and boys (versus women and girls); 64.0 % of cases (63.6 to 64.3) 64.7 % of deaths (60.8 to 70.3).** Globally, malaria cases and deaths grew rapidly from 1990 reaching a peak of 232 million cases (143 to 387) in 2003 and 1.2 million deaths (1.1 to 1.4) in 2004. Since 2004, child deaths from malaria in sub-Saharan Africa have decreased by 31.5 % (15,7 to 44.1). Outside of Africa, malaria mortality has been steadily decreasing since 1990.
Interpretation: Our estimates of the number of people living with HIV are 18.7 % smaller than UNAID's estimates in 2012. The number of people living with malaria is larger than estimated by WHO. The number of people living with HIV, **tuberculosis** or malaria have all decreased since 2000. At the global level, upward trends for malaria and HIV deaths have been reversed and declines in **tuberculosis deaths** have accelerated. 101 countries (74 of which are developing) still have increasing HIV incidence. Substantial progress since the Millennium Declaration is an encouraging sign of the effect of global action.
Comment: Good news: but with the rise in MDR-TB and XDR-TB cases, will this trend continue?

JT

Revisiting Styblo's law: could mathematical models aid in estimating incidence from prevalence data?

Begun et al Sydney, NSW, Australia

Epidemiol Infect 2014; Sept 19: 1

Abstract: Estimation of the true incidence of tuberculosis (TB) is challenging. The approach proposed by Styblo in 1985 is known to be inaccurate in the modern era where there is widespread availability of treatment for TB. This study re-examines the relationship of incidence to prevalence and other disease indicators that can be derived for surveys. We adapt a simple, previously published model that describes the epidemiology of TB in the presence of treatment to investigate a revised ratio-based approach to estimating incidence. We show that, following changes to treatment programmes for TB, the ratio of incidence to prevalence reaches an equilibrium rapidly; long before other model indicators have stabilized. We also show that this ratio relies on few parameters but is strongly dependant on, and requires knowledge of, the efficacy and timeliness of treatment.

Comment: Yet another study to show that Styblo's law is no longer helpful in estimating risk or incidence.

JT

Socio-political Issues

The liminal body: Comment on " Privacy in the context of 'Re-emergent' infectious diseases" by Justin T Denholm and Ian H Kerridge (J. Bioeth Inq 2014;11:263 – a hypothetical case about James, a contact of Susan who has active pulmonary TB).

Mason P Sydney, NSW, Australia

J Bioeth Inq 2014 Oct 31

Abstract: If James has a latent tuberculosis infection (LTBI), he is at risk of developing active tuberculosis disease but he is not yet sick.. LTBI is a liminal space between health and illness. Diagnosed with LTBI, James could be conceptualised as having a liminal body. Treatments for LTBI are available, but why would a person seek treatment for a disease he does not yet have? One thing is definite: James needs to be educated about the symptoms and severity of active tuberculosis disease.

Comment: By his name, James seems to belong to a western style Australian culture that increasingly accepts medication for risk factors, e.g. statins and anti-hypertensives. But there are people in other cultures in Australia who see this notion as creating a dangerous imbalance or disharmony.

JT

Determinates of the knowledge of and attitude towards tuberculosis in Nigeria.

Agho et al Sydney & Newcastle, NSW, Australia

J Health Popul Nutr 2014; 32: 520

Abstract: Globally, Nigeria had the fourth highest incidence of tuberculosis (TB) cases in 2009. Datasets of the Nigeria Demographic and Health Survey (NDHS) were used for examining factors associated with respondents' knowledge and attitude towards TB in Nigeria. With the same age-group of males and females, the sample included 47,193 respondents aged 15-49 years. Factors associated with the knowledge of and attitude towards TB were examined against a set of individual-, household-, and community-level variables, using multiple binary logistic regression analyses. Respondents who reported having ever heard of TB were 74.5%. Of those who ever heard of TB, 76.9% believed that TB can be cured, and 19.6 % would want a family member's TB to be kept secret. Of those who ever heard of TB, 63.1% believed that TB was spread from person to person through the air by coughing and sneezing. Multivariate analysis indicated that the probability of having poor knowledge of and negative attitude towards TB was consistently significant among the poorest (lowest wealth quintile), geopolitical regions (North Central), respondents with no schooling, non-working respondents, youngest age-group (15-19 years), and rural areas [adjusted odds ratios (AOR) = 0.76, 95% CI 0.66-0.86 for respondents who had ever heard of TB and believed that TB can be cured; AOR=0.83, 95% CI 0.73-0.94 for those who had ever heard of TB and concealed the fact that a family member had TB; and AOR=0.88, 95% CI 0.78-0.99 for those who had ever heard of TB and believed TB was spread from person to person through the air by coughing or sneezing] . Efforts to improve the knowledge of and attitude towards TB in Nigeria should focus on the youngest age-group (15-19 years), the poorest households and respondents with no schooling. Improving the knowledge and attitude of these groups of individuals may result in an increase in the number of people who will seek early treatment.

Comment: If this survey had been carried out in Australia half a century ago, I suspect the results would have been similar.

JT

What patient factors predict physicians' decisions not to treat latent tuberculosis infection in tuberculosis contacts?

Dobler et al Sydney NSW Australia

PLoS One 2013; 8: e76552

Objective: The study aimed to determine factors that are associated with physicians' decisions to offer treatment for latent tuberculosis infection (LTBI) in contacts of patients with tuberculosis.

Methods: We performed a nested case-control study in a cohort of contacts of patients with pulmonary tuberculosis who had a tuberculin skin test (TST) >/=10 mm. Cases were those who were offered treatment for LTBI. Controls were randomly selected from those who were not offered treatment for LTBI by the reviewing physician. Odds ratios were estimated by multivariate logistic regression.

Results: There were 195 cases and 279 controls. The following factors were significantly (positively or negatively) associated with being offered LTBI treatment in the multivariate analysis: female gender (OR 2.9; 95% CI 1.6-5.5), TST conversion (OR 3.9; 2.0-7.9), TST > 20 mm (OR 4.1;1.8-9.1, for TST of 21-30 mm; (2.6-23.8), for TST >30mm), sputum smear positive index case (OR 12.7; 4.5-36.1), being overseas born and immigration more than 2 years ago (OR 0.1; 0.06-0.3), being a health care worker (OR 0.2; 0.1-0.6), being a non-household contact of the TB index case (OR 0.3; 0.2-0.6) and age >35

years (OR 0.2; 0.1-0.5 for age 35 to 54.9 years and OR 0.04; 0.01-0.2 for age >/= 55 years. Previous BCG vaccine and chest x-ray findings were not significantly associated with physicians 'decision to offer treatment for LTBI.

Conclusions: Most factors that influenced physicians 'decisions on treatment for LTBI were based on evidence of an association with risk of developing TB or risk of having an adverse reaction to treatment for LTBI. However, the decreased likelihood of offering treatment for LTBI to people born overseas, men and health care workers, was apparently not based on any evidence of risk. Efforts should be made to ensure that these groups are given access to treatment for LTBI.

Comment: It is encouraging that Australian physicians recognise the link between increasing size of the Mantoux reaction and likelihood of developing TB. However a combined TST and IGRA would be preferable in diagnosing LTBI.

JT

Attitudes towards involuntary incarceration for tuberculosis: a survey of Union members.

Denholm et al Paris, France; Melbourne, Vic., Australia; New York, NY, USA; Khartoum, Sudan.

Int J Tuberc Lung Dis 2014; 18: 155

Background: Policies involving the use of involuntary incarceration for tuberculosis (TB) are highly ethically controversial. To encourage ethical reflection within the International Union against Tuberculosis and Lung Disease (The Union), the Ethics Advisory Group (EAG) surveyed members regarding their attitudes and values relating to involuntary incarceration for TB.

Methods: Members of the Union TB section were invited to respond to an anonymous web-based survey. The survey included both multiple choice questions describing a range of scenarios regarding involuntary incarceration, and free-text fields inviting respondents to provide general comments on ethical issues.

Results: The survey was completed by 194 participants, 33 (17%) of whom were opposed to involuntary incarceration on principle. The age and sex of the respondents was not associated with likelihood of principled opposition; respondents from North America were least likely to be opposed to involuntary incarceration (P=0.02). Respondents were most likely to consider involuntary incarceration for persons with known multidrug-resistant TB or a history of previous treatment default, and least likely when people lived alone, were university–educated or the main income provider for their families

Conclusion: This survey found a wide range of viewpoints regarding involuntary incarceration, and highlights a number of key elements in ethical engagement with the tensions surrounding involuntary incarceration. We provide commentary on approaches to ethical policy making in the light of these findings.

Comment: It is unfortunate that only 12% of eligible members responded to this survey, so the strength of the authors' conclusions have to be seen as less than robust. However, one could predict that TB health workers in the USA would favour involuntary incarceration.

Infection

Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study.

Denholm et al Melbourne, Vic., Australia

Drug Health Patient Saf 2014; 6: 145

Introduction: Isoniazid preventative therapy (IPT) is a widely used intervention for treatment of latent tuberculosis infection (LTBI), particularly in patients at high risk of reactivation . While treatment- limiting adverse effects have been well studied, few prospective studies have considered the range of adverse effects that patients may experience with IPT.

Methods: All patients commencing treatment for LTBI were prospectively enrolled in an ongoing database of LTBI treatment outcomes particularly related to adverse effects, treatment adherence, and treatment completion.

Results: Data on the first 100 patients who were prescribed IPT are presented. Fifty six patients reported at least one adverse event at some stage during treatment, with six experiencing at least one World Health Organization (WHO) Grade 3-4 adverse event. Increased age was significantly associated with risk of adverse effects (OR=1.05 per year; 95% CI 1.02-1.08). Eighty-five patients had documented completion of therapy locally, with ten patients ceasing IPT due to adverse effects.

Discussion: This report highlights a variety of somatic adverse effects that occurred in a real-world cohort of patients receiving. While adverse events were frequently identified in this study, the considerable majority were low grade and transient. Despite frequent adverse effects of IPT in our treatment cohort, the study demonstrated high levels of treatment adherence and completion.

Comment: A 1% rate of clinical hepatitis is about par with previous Australian experience. Without a control group it is difficult to attribute skin lesions or neuro-psychiatric symptoms to isoniazid.

JT

Screening

A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases.

Triasih et al Yogyakarta, Indonesia; Melbourne, Vic., Australia; Paris, France

Clin Infect Dis 2014; Sept 30 pii: ciu748

Background: Child tuberculosis contact screening and management can enhance case finding and prevent tuberculosis disease. It is universally recommended but rarely implemented in tuberculosis-endemic settings. The World Health Organization (WHO)-recommended symptom-based Screening approach could improve implementation but has not been prospectively evaluated.
Methods: We conducted a cohort study of children who were close contacts of pulmonary tuberculosis in Indonesia from August 2010 to December 2012. We performed clinical assessment, tuberculin skin test and chest radiography in all eligible children irrespective of symptoms at baseline. Mycobacterial culture and Xpert MTB/RIF assay were performed on sputum from children with persistent symptoms of suspected tuberculosis. Children were managed according to WHO guidelines and were prospectively followed for 12 months.
Results: A total of 269 child contacts of 140 index cases were evaluated. At baseline, 21 (8%) children had tuberculosis diagnosed clinically; an additional 102 (38%) had evidence of infection without disease.. Of children with any tuberculosis-related symptoms at baseline, 21% tuberculosis diagnosed compared with none of the asymptomatic children (P<0.001). After 12 months of follow-up, none of the 99 eligible young child contacts (<5 years) who received isoniazid preventive therapy (IPT) had developed disease compared with 4 of 149 (2.6%) asymptomatic older children who did not receive IPT.
Conclusions: Symptom-based screening is an effective and simple and simple approach to child tuberculosis contact management that can be implemented at the primary healthcare level.
Comment: But not if you add in TST and chest radiography.

JT

Molecular Biology

Draft genome sequence of a multidrug-resistant New Zealand isolate of Mycobacterium tuberculosis lineage 3.

Mac Aogain et al Dublin, Ireland; Auckland, New Zealand; Hobart, Tasmania, Australia

Genome Announc 2014; 2: 5

Abstract: Multidrug-resistance constitutes a threat worldwide to the management of tuberculosis (TB). We report the draft whole-genome sequence of a lineage 3 (East African-Indian) isolate of Mycobacterium tuberculosis which presented as multidrug-resistant in New Zealand, and describe a number of single nucleotide polymorphisms in genes relating to drug resistance.

JT

Added value of whole-genome sequencing for management of highly drug-resistant TB.

Outhred et al Sydney, NSW, Australia

J Antimicrob Chemother 2014; Dec 9: Epub

Objectives: Phenotypic drug susceptibility testing (DST) for Mycobacterium takes several weeks to complete and second-line DST is often poorly reproducible. Potentially leading to compromised clinical decisions. Following a fatal case of XDR TB, we investigated the potential benefit of using whole genome sequencing to generate an in silico drug susceptibility profile.
Methods: The clinical course of the patient was reviewed, assessing the times at which phenotypic DST data became available and changes made to the therapeutic regimen. Whole-genome sequencing was performed on the earliest available isolate and variants associated with drug resistance were identified.
Results: The final DST report, including second-line drugs, was issued 10 weeks after patient presentation and 8 weeks after initial growth of M. tuberculosis. In the interim, the patient may have received a compromised regimen that had the potential to select for further drug resistance. The in silico susceptibility profile, extrapolated from evolving evidence in the literature, provided comparable or superior data to the DST results for second-line drugs and could be generated in a much shorter time frame.
Conclusions: We propose routine whole-genome sequencing of all MDR M. tuberculosis isolates in adequately resourced settings. This will improve individual patient care, monitor transmission events and advance our understanding of resistance-associated mutations.
Comment: Certainly in XDR resistance, but how would this method compare with Xpert MDR/RIF in terms of cost and effectiveness?

JT

Immune Studies

Epitope-specific CD4+, but not CD8+, T-cell responses induced by recombinant

influenza A viruses protect against Mycobacterium tuberculosis infection.

Florida et al Sydney , NSW, Australia

Eur J Immunol 2014; Nov 28 (Epub)

Abstract: Tuberculosis remains a global health problem, in part due to the failure of the currently available vaccine, BCG, to protect adults against pulmonary forms of the disease. We explored the impact of pulmonary delivery of recombinant influenza A viruses (riAV) on the induction of Mycobacterium tuberculosis–specific CD4+ and CD8+ T-cell responses and the resultant protection against M. tuberculosis in C57BL/6 mice. Intranasal infection with irAVs expressing a CD4+ T cell epitope from the Ag85B protein (PR8.p25) or CD8+ cell epitope from the TB10.4 protein (PR8.TB10.4) generated strong T cell responses to the M. tuberculosis-specific epitopes in the lung that persisted long after the riAVs were cleared. Infection with PT8.p25 conferred protection against subsequent M. tuberculosis challenge in the lung , and this was associated with increased levels of polyfunctional CD4+ T cells at the time of challenge and during infection. Therefore, the induction of pulmonary M. tuberculosis epitope-specific CD4+, but not CD8+ T cells is essential for protection against acute M. tuberculosis infection in the lung.
Comment: We hope that human CD4+ T cells can be similarly activated.

JT

Targeting regulatory T cells to improve vaccine immunogenicity in early life.

Ndure et al The Gambia; Melbourne, Vic., Australia

Front Microbiol 2014;5: 477

Abstract: Human newborn and infants are bombarded with multiple pathogens on leaving the sterile intrauterine environment, and yet have suboptimal innate immunity and limited immunological memory, thus leading to increased susceptibility to infections in early life. They are thus the target age group for a host of vaccines against common bacterial and viral pathogens. They are also the target group for many vaccines in development, including those against **tuberculosis (TB),** malaria and HIV infection. However, neonatal and infant responses to many vaccines are suboptimal, and in the case of the polysaccharide vaccines, it has been necessary to develop the alternative conjugated formulations in order to induce immunity in early life. Immunoregulatory factors are an intrinsic component of natural immunity necessary to dampen or control immune responses, with the caveat that they may also decrease immunity to infections or lead to chronic infection. This review explores the key immunoregulatory factors at play in early life, with a particular emphasis on regulatory T cells (Tregs). It goes on to explore the role that Tregs play in limiting vaccine immunogenicity, and describes human and animal studies in which Tregs have been depleted in order to enhance vaccine responses.. A deeper understanding of the role that Tregs play in limiting or controlling vaccine-induced immunity would provide strategies to improve vaccine immunogenicity in this critical age group. New adjuvants and drugs are being developed that can transiently suppress Treg function, and their use as part of human vaccination strategies against infections is becoming a real test for the future.
Comment: Can we be sure that suppressing Tregs to increase immunity when non-living vaccines are given will apply to live vaccines?

JT

Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections.

Hodgson et al Townsville, QLD, Australia

Immunology 2014; Sep 29

Abstract: Diabetes has been recognised as an important risk factor for a variety of intracellular bacterial infections., but research into the dysregulated immune mechanisms contributing to the impaired host-pathogen interactions is in its infancy. Diabetes is characterised by a chronic state of low-grade inflammation due to activation of proinflammatory mediators and increase formation of advanced glycation end products. Increased oxidative stress also exacerbates the chronic inflammatory processes observed in diabetes. The reduced phagocytic and antibacterial activity neutrophils and macrophages provides an intracellular niche for the pathogen to replicate. Phagocytic and antibacterial dysfunction may be mediated directly through altered glucose metabolism and oxidative stress. Furthermore, impaired activation of natural killer cells contributes to decreased levels of interferon gamma, required for promoting macrophage antibacterial mechanisms. Together with impaired dendritic cell function, this impedes timely activation of adaptive immune responses. Increased intracellular oxidation of antigen presenting cells in individuals with diabetes alters the cytokine profile generated and the subsequent balance of T cell immunity. The establishment of acute intracellular bacterial infections in the diabetic host is associated with impaired T-cell mediated immune responses. Concomitant to the greater intracellular bacterial burden and potential cumulative effect of chronic inflammatory processes, late hyperinflammatory cytokine responses are often observed in individuals with diabetes, contributing to systemic pathology. The convergence of intracellular bacterial infections

and diabetes poses new challenges for immunologists, providing the impetus for multidisciplinary research.
Comment: The two diseases most associated with diabetes and intracellular bacteria in Australia are of course tuberculosis and melioidosis. Yet there does not seem to be an association between diabetes and other mycobacterial diseases.

JT

Children

Bacillus Calmette-Guerin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system.

Clothier et al Melbourne, Vic., Australia

Drug Saf 2014; Dec 5: Epub

Background: Bacillus Calmette-Guerin (BCG) vaccine is used worldwide, with high efficacy against childhood Mycobacterium tuberculosis (TB) meningitis and miliary TB. BCG vaccine is considered safe, with serious systematic adverse events following immunization (AEFI) of immunocompetent recipients being rare, although adverse event rates vary between differing BCG strains. In Victoria, Australia, AEFI are reported to SAEVIC (Surveillance of Adverse Events following Vaccination in the Community), an enhanced passive surveillance system operational since 2007.
Objective: To describe the epidemiology of reported BCG AEFI in Victoria, Australia, particularly following the recall of Connaught BCG vaccine, substitution with Denmark-SSI vaccine and subsequent program delivery adjustments.
Methods: Retrospective analysis of reported BCG AEFI in Victoria, Australia, for the 6-year period 2008-2013. Incidence rates were calculated using available doses-distributed, doses-administered and population data denominators with 95% confidence intervals.
Results: The predominant BCG AEFI reported were abscess and lymphadenopathy, with higher reports for males than for females (p=0.039). The rates of AEFI per 10,000 doses distributed were similar for the Connaught and Denmark-SSI strains, at 11.6 and 15.4, respectively (p=0.414). When doses administered rather than doses distributed were considered, the rate of reported Denmark-SSI AEFI was much higher, at 62.8 per 10,000 doses administered. Meaningful result interpretation was hampered by a lack of a BCG vaccination register, multiple disparate providers and absent doses-administered prior to the recall.
Conclusion: Effective AEFI surveillance is of paramount importance as countries are faced with unplanned vaccine strain changes following the 2012 BCG recall and subsequent global vaccine supply shortages. The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programs worldwide to review AEFI surveillance systems.
Comment: The AEFI rates for Denmark-SSI strains administered, do not seem excessive compared to those among Aboriginal and Torres Strait Islander babies using the old CSL vaccine.

Microbiology

Practical biosafety in the tuberculosis laboratory: containment at the source is what truly counts.

Van Soolingen et al Bilthoven, Lelystad, Meibergdrief, Enschede, The Netherlands, Adelaide, SA, Australia, Geneva, Switzerland.

Int J Tuber Lung Dis 2014; 18: 885

Abstract: In industrialized countries, sufficient resources for establishing and maintaining fully equipped biosafety level 3 (BSL-3) laboratories according to international standards are generally available. BSL-3 laboratories are designed to provide several layers of containment to protect the laboratory worker as well as the outside environment and community from risk of exposure in case of local contamination. However, such facilities are scarce in high-burden settings, primarily due to high financial burden and complexity of the initial construction and/or regular maintenance. Measures to prevent unintended exposure to Mycobacterium tuberculosis during laboratory manipulation of specimens and cultures is the first, and by far the most important, aspect of containment. This paper focuses on the need for risk containment at source. Assuming that in many settings the establishment of BSL-3 laboratories with all the required features is not achievable, this paper also discusses the minimum requirement necessary to mitigate risks associated with particular laboratory procedures. The term ' TB containment laboratory' is used throughout this paper to describe the minimum requirements for a laboratory suitable for high-risk procedures. The TB containment laboratory has many, but not all, of the features of a BSL-3 laboratory.
Comment: It is interesting that the authors do not regard cross-contamination of specimens as even more important than contamination of laboratory staff.

JT

Non-Tuberculous Mycobacteria

Heterogeneity of clinical and environmental isolates of Mycobacterium fortuitum using repetitive element sequence-based PCR: municipal water an unlikely source of community-acquired infections.

Thomson et al Brisbane, Qld, Australia

Epidemiol Infect 2014; 142: 2057

Abstract: M. fortuitum is a rapidly growing mycobacterium associated with community-acquired and nosocomial wound, soft tissue and pulmonary infections. It has been postulated that water has been the source of infection especially in the hospital setting. The aim of this study was to determine if municipal water may be the source of community-acquired or nosocomial infections in the Brisbane area. Between 2007 and 2009, 20 strains of M. fortuitum were recovered from municipal water and 53 patients' isolates were submitted to the reference laboratory. A wide variation in strain types was identified using repetitive element sequence-based PCR, with 13 clusters of >/= 2 indistinguishable isolates, and 28 patterns consisting of individual isolates. The clusters could be grouped into seven similar groups (>95% similarity). Municipal water and clinical isolates collected during the same time period and from the same geographical area consisted of different strain types, making municipal water an unlikely source of sporadic human infection.
Comment: A reassuring report.

JT

TB and HIV

Latent tuberculosis screening using interferon-gamma release assays in an Australian HIV-infected cohort: is routine screening worthwhile?

Doyle et al Melbourne, Vic., Australia

J Acquir Immune Defic Syndr 2014; 66: 48

Background: There are limited data from high-income countries on the performance of interferon-gamma release assays in screening for latent tuberculosis infection (LTBI). We analyzed the routine application of the Quantiferon-TB Gold (QFT-G) assay to detect and predict latent and active TB among HIV-infected patients in Australia.
Methods: A retrospective cohort study included all HIV-infected patients attending the Melbourne Sexual Health Service between March 2003 and February 2011 who were screened for LTBI using QFT-G. Clinical data were analyzed in multivariable models to determine predictors for QFT-G positivity using logistic regression and active TB development using Cox proportional hazards.
Results: Nine hundred seventeen HIV-infected patients had >/= 1 QFT-G performed, of whom 884 (96.4%)were negative, 29 (3.2%) positive and 4 (0.4%) indeterminate. The mean age was 40.9 years and 88% were male, with median follow-up of 26.4 (interquartile range 15.4-30.7) months. Five hundred fifty (63%) were Australian born, whereas 198 (23%) were born in Asia or Africa. QFT-G was positive in 2.0 % of Australian born, 5.3% of overseas-born [OR: 2.6, 95% CI 1.2-5.6, P=0.017]. and 12.7% of African-born patients (OR: 7.1, 95% CI 2.9-17.3, P<0.001). Two cases of culture-positive TB occurred after QFT-G screening in 3.4% of QFT-G positive and 0.1 % of QFT-G negative patients (adjusted HR: 42.4, 95%CI: 2.2-827, P=0.013), rate of 111 (95% CI: 27.8-445) per 100,000 person-years.
Conclusions: In this context, QFT-G has a high negative predictive value (99.9%) with few indeterminate results. A risk stratification to LTBI screening, where HIV-infected patients with epidemiological risk factors for infection undergo QFT-G testing, might be clinically appropriate and potentially cost effective in similar settings.
Comment: Agreed, but in 2015, such a selected sample needs to have both QFT-G (or GIT) and TST administered at the same time to achieve a more accurate diagnosis of infection.

JT

Diagnosis

Commercial nucleic acid amplification tests in tuberculous meningitis- a meta-analysis.

Solomons et al Tygerberg, Cape, South Africa; Amsterdam, The Netherlands; Sydney, NSW, Australia.

Diagn Microbiol Infect Dis 2014; 78: 398

Abstract: Although nucleic acid amplification tests (NAATs) promise a rapid, definitive diagnosis of tuberculous meningitis, the performance of first-generation NAATs was suboptimal and variable.
We conducted a meta-analysis of studies published between 2003 and 2013, using the Quality Assessment of Diagnostic Accuracy-2 (Quadas-2) tool to evaluate methodological quality. The diagnostic accuracy of newer commercial NAATs was assessed. Pooled estimates of diagnostic accuracy for commercial NAATs measured against a cerebrospinal fluid Mycobacterium tuberculosis culture-positive gold standard. were sensitivity 0.64. specificity 0.98 and diagnostic odds ratio 64.0. Heterogeneity was limited; P value= 0.147 and I (2)= 33.85. The Xpert MTB/RIF ® test was evaluated in 1

retrospective study and 4 prospective studies, with pooled sensitivity 0.70 and specificity 0.97. The Qadas-2 tool revealed low risk of bias, as well as low concerns regarding applicability. Heterogeneity was pronounced among studies of in-house tests. Commercial NAATs proved to be highly specific with greatly reduced heterogeneity compared to in-house tests. Suboptimal sensitivity remains a limitation.
Comment. Sadly, the sensitivity of CSF culture for Mtb could also be improved.

JT

Pulmonary involvement in patients presenting with extra-pulmonary tuberculosis: thinking beyond a normal chest x-ray.

Herath et al Auckland New Zealand.

J Prim Health Care 2014; 6: 64

Introduction: Recognition of pulmonary involvement in extra-pulmonary tuberculosis (TB) may be an important public health issue, as smear-negative pulmonary TB is responsible for about 17% of new infections. Pulmonary TB can be present despite a normal chest x-ray (CXR), even in human immunodeficiency (HIV)-negative patients. In this retrospective clinical audit, we reviewed a case series of HIV-negative patients with extra-pulmonary tuberculosis to identify the proportion with concurrent pulmonary TB despite an unremarkable CXR.
Methods: Clinical notes, microbiology results and CXR reports were reviewed from consecutive patients treated at Auckland City Hospital for extrapulmonary TB from January 2007 to July 2010.
Results: Of the sample of 103 patients with extra-pulmonary TB, the majority of patients were born in an Asian country (n=70; 68%). The commonest presentation of extra-pulmonary TB was lymphadenopathy (n=51; 50%), followed by pleural (n=24; 23%) and bone (n=6; 6%) disease. Extra-pulmonary TB was diagnosed by biopsy or excision of the extra-pulmonary site in the majority (n=74; 72%), and by sputum testing alone in 26(25%). The majority had CXR abnormalities (n=76; 74%). In the group with a normal CXR (n=27), 55%: n=15) had sputum cultures performed. In total, 18% (n=5) of patients with extra-pulmonary TB and a normal CXR had pulmonary TB, of whom two were smear positive.
Discussion: In patients with extra-pulmonary TB, sputum testing should be considered to detect concurrent pulmonary TB even if a CXR is normal, especially in immunosuppressed or symptomatic patients. This may aid diagnosis and determine infectivity and consequent public health action.
Comment: Agreed, but what if the patient with a normal CXR has no sputum? Does one go down the road of sputum induction and even proceed to bronchoscopy or resort to more imaging in the form of thin slice chest CT?

JT

Pharmacology

Efficient synthesis and anti-tubercular activity of a series of spirocytes: an exercise in open science.

Badiola et al Sydney, NSW, Australia

PLoS One 2014; 9: e111782

Abstract: Tuberculosis afflicts an estimated 2 billion people worldwide and causes 1.3 million deaths annually. Chemotherapeutic solutions rely on drugs developed many years ago, with only one new therapeutic having been approved in the past 40 years. Given the rise of drug-resistant strains, there is urgent need for the development of a more robust drug development pipeline. Glaxo Smith Kline recently placed the structure and activities of 177 novel anti-tubercular leads in the public domain, as well as the results of ongoing optimization of some of the series. Since many of the compounds arose from screening programs, their provenance was unclear and synthetic routes were in many cases not reported. Here we present the efficient synthesis of several novel analogues of one family of the GSK compounds-termed “Spiros”- using an oxa-Pictet-Spengler reaction. The new compounds are attractive from a medicinal chemistry standpoint and some were potent against the virulent strain, suggesting this class is worthy of further study. The research was carried out using open source methodology, providing the community with full access to all raw experimental data in real time.
Comment: Such transparency should be a good thing, but in drug development will it give the community unrealistic expectations?

JT

Cavitating Pulmonary TB (courtesy IUAT&LD)