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Inside this issue: Tuberculosis

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In this issue we feature 3 important systematic reviews, a Cochrane review of GeneXpert in diagnosing rifampicin resistance, the use of BCG for tuberculosis in children and the association of HIV and MDR TB. We likewise reviewed several innovative articles featuring a candidate TB vaccine (MVA85A) delivered by unique aerosol route as well as 2 benchmark molecular TB studies on PZA/aspartate decarboxylase (Pan D) as a new target for further drug development and new rpoB mutations in the mycobacteria as a cause of rifampin resistance. This issue also features the latest published clinical trials on 3 new promising drugs on the horizon 2 being used especially for MDR TB (linezolid and Bedaquiline) and a drug shortening (moxifloxacin) regimen in the treatment for drug sensitive TB. New approaches to an old disease and a better understanding old reliable therapies and vaccines show the battle against TB involving new tools will be fought along many fronts with its many hits and misses. As we begin to unravel the mysteries of the mycobacterium and how and why our drugs work against it, breakthroughs and an explosion of TB research is inevitable as the quest for TB control in high-burden countries and TB elimination in others marches on. **CY, JB, RP, FF.**

Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults.

Authors: Steingart KR et al.

Reference: Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD009593. DOI:10.1002/14651858.CD009593.pub3.

URL: *http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009593.pub3/pdf*

Comments (by RP): The review shows that Xpert® MTB/RIF assay is better than direct sputum microscopy (DSM) in the detection of TB, it improves DSM by 23%. It still cannot totally replace the DSM due to the large amount of money needed to put up the assay test. In clinical practice its value could be placed in confirming the diagnosis of TB and also in smear negative patients who needs immediate initiation of treatment. It is still not the ideal test in the detection of drug resistance as it only detects Rifampicin resistance but it can be used as an initial guide in the initiation of treatment for MDR-TB while waiting and adjusting the treatment based on the results of the conventional TB culture and sensitivity testing. Clinicians would also be looking for studies using the assay in specimens where detection of TB is much needed (e.g. pleural fluid, CSF, peritoneal fluid).

Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis.

Authors: Roy A et al.

Reference: BMJ 2014; 349:g4643 doi: 10.1136/bmj.g4643 (published 5 August 2014)

URL: http://www.bmj.com/content/349/bmj.g4643

Comments (by JB): This systematic review and meta-analysis demonstrated the efficacy of BCG vaccination in protecting against infection in settings where children are presumed to have been exposed to an infectious case of TB. This finding was possible since the articles included were mainly outbreak investigations and contact tracings. The authors' extensive search was commendable with the final 14 included studies mostly rated to be of moderate to high quality based on a modified Newcastle-Ottawa scale. However, it was mentioned that seven articles were not included for failure of the authors to provide the research team with the needed raw data. The potential effect of their exclusion was not elucidated. This review also provided a perspective on how BCG vaccination works. Other findings like the effect of latitude may need additional studies to be confirmed as most articles that addressed this are limited. The potential effects of differences in exposure as well as the age of vaccination were admittedly some of the limitations of this review. Although there was no difference in efficacy demonstrated in relation to vaccination policy, implications on this subject might be different considering the incidence and burden of TB for each country. For high burden countries, policy on BCG vaccination may be rational.

Association between HIV/AIDS and Multi-Drug Resistance Tuberculosis: A Systematic Review and Meta-Analysis.

Authors: Mesfin Yonatan Moges et al.

Reference: PLoS ONE 9(2): e89709 Pub. Jan. 8,2014 DOI: 10.1371/journal.pone.0082235

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3885391/

Comments (by CY): This systematic review shows a positive though surprisingly weak (odds ratio 1.24, 95%CI 1.04-1.43) correlation between HIV and MDR though conventional wisdom would have expected the association to be higher. It also showed that primary TB resistance correlated more strongly with HIV, as well as in population-based surveys with no correlation at all in institution-based studies. The met-analysis was heavily biased in favor of institution based ob-

servational studies (22/24) with only 2 population based studies. Authors noted that if only the larger studies were included the confidence interval would have approached the 1.01 lower limit, approaching no statistical significance. Also while the distribution of the studies using traditional funnel plot showed symmetrical distribution of effect estimate and Beg rank correlation statistic (p = 0.33) showed no evidence of publication bias which means the funnel plot analysis seems cursorily and statistically acceptable, scanning the review articles seem show the absence of studies from India and China where both MDR TB and HIV are highly prevalent although there are 2 mentioned studies from Thailand (Bangkok and northern Thailand). The Egger weighted regression analysis (p = 0.02) showed possible presence of publication bias. More population-based studies particularly in high-burden countries in the Asia-Pacific region should strengthen the validity of this study.

Linezolid in the treatment of extensively drug-resistant tuberculosis.

Authors: Zhang L et al.
Reference: Infection August 2014, Volume 42, Issue 4, pp 705-711
URL: http://link.springer.com/article/10.1007%2Fs15010-014-0632-2
Comments (by RP): This case-control study showed a success rate of 60% (9/15) for those XDR TB patients exposed to linezolid, which is higher compared to the 34.9% overall success rate for the cohort group. While this may provide some proof of efficacy for linezolid in XDR TB , there is also a high degree of identified resistance of 26.7% (4/11) to linezolid. It is also important to note that 2 patients who showed sensitivity to linezolid had an unfavorable treatment outcome. A cost-analysis among the treatment options in this study would also provide further information on the benefit of using linezolid.

Safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol in BCG-vaccinated healthy adults: a phase 1, double-blind, randomised controlled trial.

Authors: Satti I et al.

Reference: Lancet Infect Dis 2014 published online August 21, 2014

URL: http://dx.doi.org/10.1016/S1473-3099(14)70845-X

Comments (by JB): This is a very interesting study exploring the innovative strategy of a vaccine delivered via the aerosol route that may enhance local protective immune responses at the primary site of TB infection. It was demonstrated that this route of MVA85A vaccine administration was safe and that the levels of important immune markers were high in both blood and BAL fluid samples. Further studies may be recommended to further explore the immune responses at the systemic and mucosal level especially to both insert and vector of this vaccine. In addition, its main positioning vis-a-vis BCG vaccination should be elucidated.

Aspartate decarboxylase (PanD) as a new target of pyrazinamide in Mycobacterium tuberculosis.

Authors: Shi W et al.

Reference: Emerging Microbes & Infections (2014) 3, e58; doi:10.1038/emi.2014.61 Published online 13 August 2014

URL: http://www.nature.com/emi/journal/v3/n8/full/emi201461a.html

Comments (by CY): "There is significant recent interest in understanding PZA, since it is the only TB drug that cannot be replaced without compromising the efficacy of the therapy, so it is indispensible," said Ying Zhang, MD, PhD, senior author of the study and professor in the Bloomberg School's W. Harry Feinstone Department of Molecular Microbiology and Immunology. "The process of identifying the correct resistance mutations was quite tedious and took about two years to complete. However, the work led to the identification of a potential new mechanism of PZA resistance."

The current study suggests that mutations in the panD gene may also be involved. PanD encodes aspartate decarboxylase, which is involved in synthesis of the amino acid β-alanine, a precursor for pantothenate (which is vitamin B5) and co-enzyme A biosynthesis. The panD mutations were identified not only in mutants isolated from *in vitro* but also in clinical isolates such

as in the naturally PZA-resistant bacterium M. canettii strain and in a PZA-resistant MDR-TB strain.

PZA is an old reliable first-line TBA drug is also used in MDR TB. As authors Zhang and his colleagues highlighted, " we believe panD could be a potential target for new antibiotic therapies" opening up new avenues in developing future TB drugs especially to shorten therapy and to combat MDR-TB.

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline.

Authors: Diacon A et al.

Reference: New England J Med 2014; 371:723-732 August 21, 2014 DOI: 10.1056/NEJMoa1313865

URL: *http://www.nejm.org/doi/pdf/10.1056/NEJMoa1313865*

Comments (by CY): Bedaquiline is one of the first of the new-generation novel TB drugs that have been developed specifically to target MDR- TB. This phase 2 trial with outcomes at 6 months and 120 weeks shows great promise in adding to our armamentarium of new tools and drugs against TB. The study however cites that there were 10 deaths in the Bedaquiline group versus placebo and this is a cause for concern on the possible long-term safety profile of the new drug especially when combined with already clinically complex and toxic second-line TB drugs. There is probably a need to dig further in analyzing these subgroup especially when larger phase 3 trials are concluded soon. Interestingly, when these new class of drugs are combined together, as proposed in some forthcoming studies, it would be interesting to know their applications in both drug sensitive and drug resistant TB and whether they can eventually lead to shortening the long treatment in tuberculosis.

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis.

Authors: Gillepsie SH et al.

Reference: N Engl J Med 2014 Sept 7 DOI: 10.1056/NEJMoa1407426

URL: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1407426

Comments (by FF): In this well designed study, shortening of treatment course using moxifloxacin-based regimen which was seen in the murine model to be effective did not work adequately underscoring the need for further study in the selection of drug regimen in drug development for active tuberculosis. Other aspects for favorable treatment outcome should be weighed, particularly better treatment adherence, which in this study was based on receipt of approximately 80% of assigned regimen. Although adverse events were similar among the study group, the potential resistance development still raises some discomfort for using moxifloxacin as first line treatment based on the above outcome since this drug is also used for the treatment of multi-drug resistant tuberculosis.

A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control.

Authors: Churchyard GJ et al.

Reference: N Engl J Med Jan 23, 2014; 370:4: 301-310

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1214289

Comments (by FF): As recognized by the authors, the isoniazid intervention in this study was suboptimal and there were a lot of confounders that would favor re-infection such as the living condition of the miners and relatively high prevalence of silicosis and HIV. In an ideal setting, the prompt and adequate case finding and case holding together with an optimal preventive therapy are still the keys to successful tuberculosis control. In the meantime, isoniazid preventive therapy still has a role among specific group of patients and maybe a continuous isoniazid preventive therapy should be considered in highly endemic areas.

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More in Respirology: FREE “Topic in Focus”:
Tuberculosis: Current state of knowledge.

Detection of Mutations in rpob Gene of Clinically Isolated M. tuberculosis by DNA Sequencing.

Authors: Sharma S and Madan M

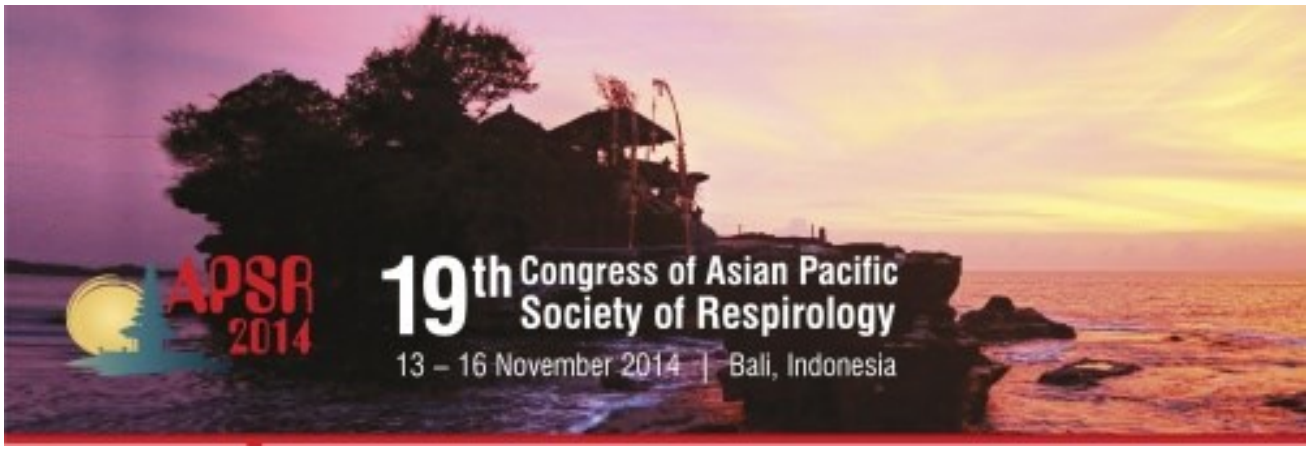
Reference: Journal of Mycobacterial Disease 2014: 4:4. May 30, 2014

URL: http://dx.doi.org/10.4172/2161-1068.

Comments (by CY): Despite the large number of mutations already reported in other similar studies, the evidence of new mutations in this study is a cause for great concern for TB control, it indicates that mutations continue to arise, probably due to the ability of M. tuberculosis to adapt to drug exposure as cited by the authors of this study.

For the control of MDR–TB, elimination of uncompleted treatment or poor adherence is critical which is challenging in the face of usually 18-24 months of therapy. This is made more alarming by the recent rising default rates even in well-established MDR/PMDT treatment centers in high -burden countries approaching 30% or more. The authors also highlighted that since incomplete treatment tends to facilitate the rate of evolution of increased levels of drug resistance within MDR-TB clones which facilitates increase in prevalence of such clones in M. tuberculosis populations, treatment becomes more difficult, which makes non-compliance more likely, and therefore uncompleted treatments more likely, which completes a vicious self-accelerating cycle. This possibility of uncompleted treatments resulting in escalating rise in prevalence and strength of MDR-TB means that every case of uncompleted treatment counts, and should be avoided if man is to stem the MDR-TB tide. Hence, early detection of the MDRTB may well be critical to durable control of tuberculosis. This basic benchmark molecular epidemiologic TB study as well as many similar studies currently underway will help researchers as well as clinicians combat TB, especially MDR TB.

Looking forward to seeing you in Bali for the APSR 2014!



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