Assessing impact of Isoniazid as early preventive therapy for non-HIV population in Malaysia: an age-structured model

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Background: Tuberculosis remains as one of the highest unresolved disease burden among re-emerging diseases in Malaysia for the last thirty years. Since 1980’s, Isoniazid Preventive Therapy has been adopted for paediatric population in Malaysia. More recently, it has been extended to the people living with HIV. With current treatment protocol emphasizing among the infectives, we seek to find if combination treatment of these active cases with Isoniazid preventive therapy for other high risk latent tuberculosis infection groups among non-HIV population would give greater impact on reducing incidence.

Methods: This study aims to apply the use of infectious disease modelling to study the progression of latent tuberculosis infection among non-HIV population in Malaysia, and to assess the impact of Isoniazid as preventive therapy on reducing incidence. We present a deterministic compartmental age-structured tuberculosis model which incorporates treatment of infectives as well as the preventive therapy. The model assumes latently infected individuals develop active disease as a result of primary infection, endogenous reactivation and exogenous reinfection. We start by formulating and analyzing the model without any intervention strategy then, we extend to incorporate the preventive therapy and treatment of infectives. The epidemic thresholds known as reproduction numbers and equilibria for the model were determined, and stabilities analyzed. The reproduction numbers for the model were compared to assess the possible community benefits achieved by treatment of infectives, preventive therapy and a holistic approach of combination of both intervention strategies. The model then further quantifies the effectiveness of preventive therapy for early latent tuberculosis infection and demonstrates how effective the therapy has to be to eliminate tuberculosis, when use in conjunction with treatment for active tuberculosis.

Results: The analysis shows that additional coverage and treatment of infectives among non-HIV population is more effective in the first years of implementation of this preventive therapy as treatment results in clearing active tuberculosis immediately and there after preventive therapy will do better in controlling number of infectives due to reduced progression to infectious state.

Conclusion: Our model suggests that Isoniazid Preventive Therapy which identify and treat persons recently infected may have a substantial effect on controlling tuberculosis epidemics in Malaysia.

Drug repositioning of latent TB

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Background: Mycobacterium tuberculosis (Mt), the aetiologic agent of tuberculosis, kills about 1.7 million people per year and is present in a latent form in about one-third of world’s population. Glycosyltransferases and Glycosyl hydrolases catalyse the synthesis of important glycoconjugates, including glycolipids (PIM, LAM, and AG), glycoproteins, and polysaccharides offer the suitable drug targets. Drug repositioning provides immense opportunity and provides solutions for increasing time, cost and failure of novel drug discovery process. The pharmaceutical companies showed less interest in TB due to less profit in marketing and huge cost of developing a drug. Hence drug repositioning can be a alternative way to fight against TB.

Here we have used computational functional genomics method to predict the novel carbohydrate active enzymes from Mt genome, followed by drug repositioning of the selected genes based on their involvement in TB latency.

Methods: The functional re-annotation of glycogenome of M.tuberculosis H37Rv on computational functional genomics, fold recognition methods was performed. 14 glycome related genes reported as top 500 ranked genes in latency by TargetDB (Dac B1, PurF, Rv0486, Rv0648, Rv1082, Rv1090, Rv1170, Rv1987, Rv2006, Rv2188c, Rv2402, Rv3487c, Rv1922, and Rv2619c) were selected. The structure of the proteins was modelled using Modeler 9v9. The network of TB co-infection with other diseases based on the epidemiological literature available between year 1966-2012 was created using Cytoscape and drugs used for those indications were used for docking analysis.

Results: The functional re-annotation of glycogenome of M.tuberculosis H37Rv revealed ~260 new glycome related genes including several GTs, GH, and secreted glycoproteins important for cell wall biosynthesis, virulence and other cellular metabolism. The epidemiological data suggested co-existence and reactivation of latent tuberculosis during chronic disorders and immunocompromised individuals with opportunistic infections. The anti-diabetic drugs, nucleotide analogs used for cancer treatment, HIV, protozoan disease showed novel interaction with the TB drug targets.

Conclusion: The chance of Disease-Target-Drug interaction during this co-infection was more and exemplifies the survival strategy of tuberculosis infection. This knowledge driven drug repositioning strategy following understanding of interacting diseases can be effectively applied for the treatment for tuberculosis.

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