Impact of patient non-compliance on tuberculosis treatment regimens

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Introduction

Tuberculosis is a leading cause of death in the world today and infects about one third of the world's population. WHO currently recommends a standard treatment for TB consisting of multiple drugs. Alternative drug combinations are also being investigated as possible regimens. Although the current standard treatment is fairly effective, due to factors including the long treatment time of tuberculosis, many patients do not follow the entire treatment regimen. This non-compliance could lead to the relapse of the patient and the emergence of resistance to anti-TB drugs.

Possible Treatment Regimens

- Standard - 8 weeks of isoniazid, rifampin, pyrazinamide, and ethambutol and 18 weeks of isoniazid and rifampin daily
- Remox 1 - 8 weeks of moxifloxacin, isoniazid, rifampin, and pyrazinamide and 9 weeks of moxifloxacin, isoniazid, and rifampin daily
- Remox 2 - 8 weeks of ethambutol, moxifloxacin, rifampin, and pyrazinamide and 9 weeks of moxifloxacin and rifampin daily

Objective

To use a mathematical model that simulates TB drug treatment and patient non-compliance to investigate the effect of patient compliance with the three TB treatment regimens a percentage of the time.

TB and drug dynamics model

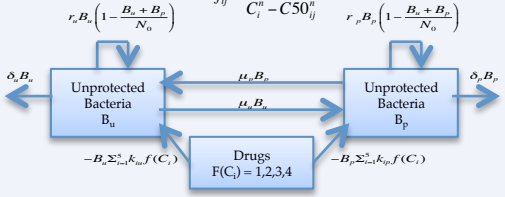
$$\dot{B}_u = r_u B_u (1 - \frac{B_u + B_p}{N_o}) - \delta_u B_u - \mu_u B_u + \mu_p B_p - \Sigma f_{iu} B_u$$

$$\dot{B}_p = r_p B_p (1 - \frac{B_u + B_p}{N_o}) - \delta_p B_p - \mu_p B_p + \mu_u B_u - \Sigma f_{ip} B_p$$

$$\dot{C}_i = -d_i C_i$$

$$C_i(t) = C_i(t) + C0_i$$

$$f_{ij} = \frac{k_{ij} C_i^n}{C_i^n - C50_{ij}^n}$$



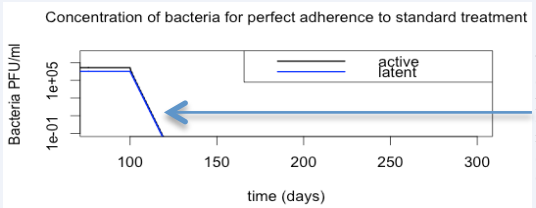
Non-compliance simulation

We created 1000 patients with the computer. For each patient, values of the model parameters were sampled from a range of reasonable values. We then simulated TB and drug dynamics for each patient. To model non-compliance, we randomly allowed our simulated patients to skip a dose with a specified probability.

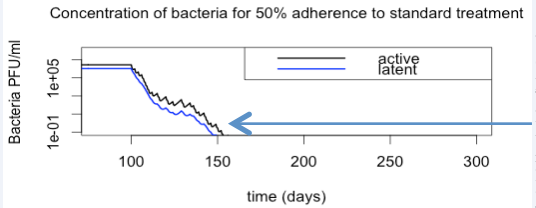
We ran the simulation until the end of the treatment and then recorded levels of bacteria. We considered treatment a success if <1 bacteria was present, an apparent failure >100 bacteria and an inapparent failure (looks like cure but is not) in between. We recorded the percentages of each outcome for each level of non-compliance and treatment regimen.

Results I

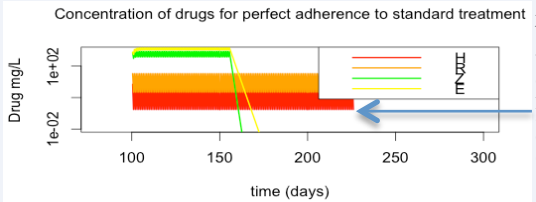
The following graphs show examples of the time series of the bacteria and the drug for the standard treatment regimen at perfect adherence and 50% adherence.



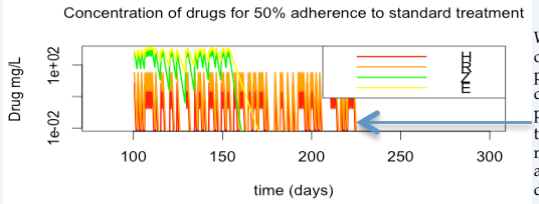
When patient compliance is perfect, the amount of bacteria in the patient decreases consistently.



When the compliance is not perfect, the bacteria is not killed and grows when the drug is not taken, and the lines representing the amount of bacteria is more jagged.



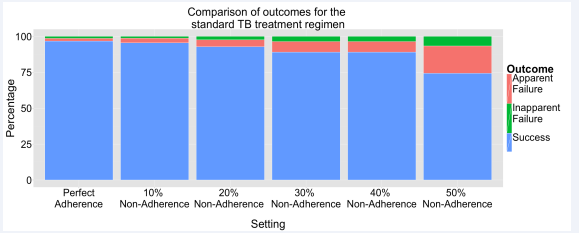
When patient compliance is perfect, the amount of drugs is consistent each day.

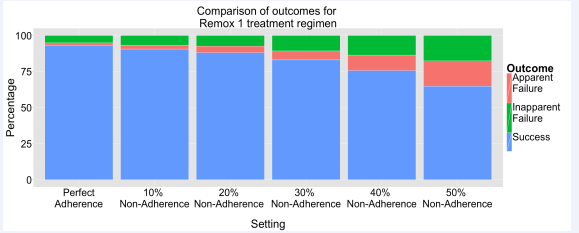


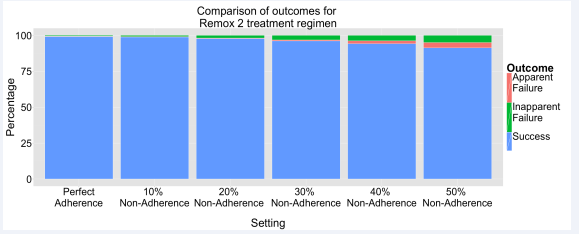
When the compliance is not perfect, there are days when the patient skips taking their medicine and the amount of drugs decreases.

Results II

The graphs below show comparisons of the number of successes (<1 bacteria), inapparent failures (>1 and <100 bacteria) and apparent failures (>100 bacteria) for each treatment regimen at different percentages (100% - 50%) of adherence.







Conclusion

As the compliance to each treatment regimen decreases, the number of treatment success of each regimen also decreases. Remox 1 demonstrated the most number of treatment failures, while Remox 2 showed the least number of failures. Also, the differences among the number of failures as compliance to Remox 2 decreased were not as great as the differences among the number of failures to the standard treatment and Remox 1. This suggests that Remox 2 might be more forgiving towards patient non-compliance than the other two regimens.

In the future, more possible treatment regimens should be added to the model as well as other possible sources of non-compliance such as increasing non-compliance as the number of bacteria decreases and TB symptoms disappear..