Modeling the Treatment of Within-Host Active and Latent Tuberculosis

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Overview

- 2 billion people infected; 8-10 million new cases per year; 1-3 million deaths per year
- Standard treatment: 2 months Isoniazid (H), Rifampin (R/RIF), Ethambutol (E), and Pyrazinamide (Z), 4 months Isoniazid and Rifampin (2HRZE/4HR) daily or 3 /week

Objective

- Make predictions for TB treatment regimens:
  - Create a mathematical model to simulate all four drugs
  - Examine different drugs: how to best eliminate active and latent TB and shorten treatment time
  - Investigate non-adherence to therapy

Model Description

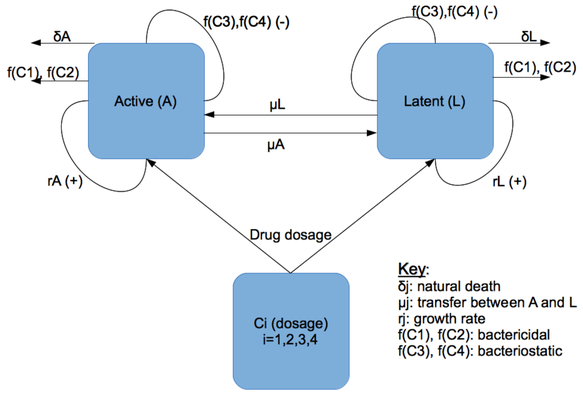

Figure 1: *Flow diagram of our compartment model.*

$$\dot{C}_i = -d_i C_i, C(t) = C(t) + C_{i,0} \text{ every T hours, for } i = 1,2,3,4 \quad (1)$$

$$\dot{B}_A = r_A B_A(1 - \frac{B_A + B_L}{N_0})(1 - f(C_3))(1 - f(C_4)) - B_A(k_{1,A}f(C_1) + k_{2,A}f(C_2)) - \delta_A B_A - \mu_A B_A + \mu_L B_L \quad (2)$$

$$\dot{B}_L = r_L B_L(1 - \frac{B_A + B_L}{N_0})(1 - f(C_3))(1 - f(C_4)) - B_L(k_{1,L}f(C_1) + k_{2,L}f(C_2)) - \delta_L B_L - \mu_L B_L + \mu_A B_A \quad (3)$$

$$f(Ci) = \frac{C_i}{C_i + C_{i,50}}, \text{ for } i = 1,2,3,4 \quad (4)$$

Model Details:

- Active: fast growing, exposed to drugs; Latent: slow growing, more protected
- Isoniazid (C_1) and Rifampin (C_2) are bactericidal (actively kill bacteria)
- Ethambutol (C_3) and Pyrazinamide (C_4) are bacteriostatic (inhibit bacteria growth)
- We used random parameter sampling to recreate patient variability
- If bacteria load (X)<1, then treatment success. If 1<X<detection, then inapparent treatment failure. If detection<X, then apparent treatment failure.

Model Confirmations

We compared our model with experimental results produced from sputum samples. Sputum samples detect active TB bacteria, but may or may not detect latent bacteria. Our model matched data by Joloba et al. [1] well; both data sets fall below one around day 60.

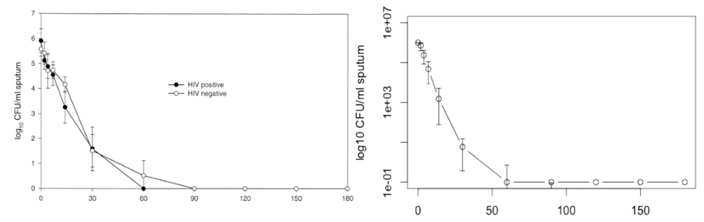

Figure 2: *Left: Data produced by Joloba et al. on amount of sputum produced at various stages of standard therapy for 22 non-HIV patients. Right: Our model.*

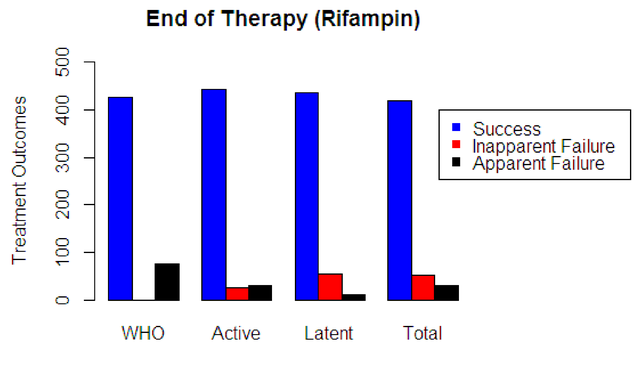

Figure 3: *Results of standard therapy for 500 simulations. For active bacteria, 89% of the runs were treatment success, 5% were inapparent failure, and 6% were apparent failure. For total bacteria, 84% were treatment success, 10% were inapparent failure, and 6% were apparent failure. These numbers compare with 2010 WHO data of 85% treatment success [2].*

Model Predictions

In our model, we replaced rifampin with rifabutin (RBN), another first line drug recently off patent, making it a viable option. Rifabutin has a longer half-life and a lower dosage than rifampin.

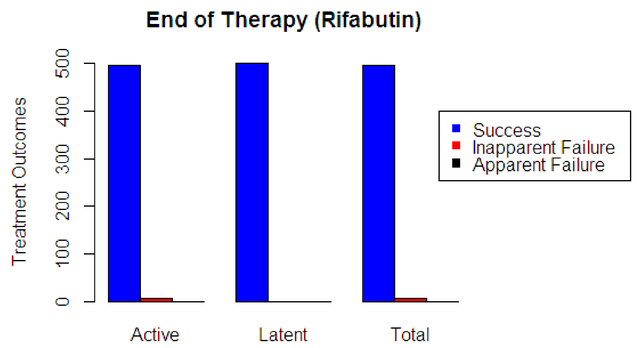

Figure 4: *Results of 500 simulations with rifabutin instead of rifampin. We achieve 99% treatment success and 0% treatment failure. The average time for bacteria clearance was 50 days.*

We also replaced rifampin with a theoretical drug possessing ideal parameters to optimize bacteria clearance at a low dosage.

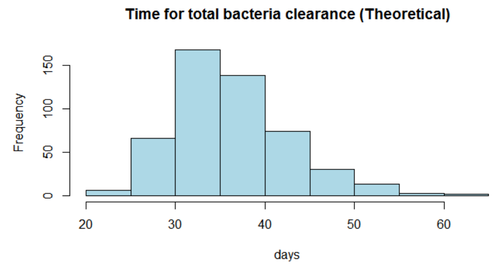

Figure 5: *Results of 500 runs with our theoretical drug. We achieve 100% treatment success and average time for bacteria clearance was 37 days.*

Finally, we looked at non-adherence (Fig. 6). With a 16% chance of not medicating per day [3], the rifampin success rate fell 11%, rifabutin fell 5%, and the theoretical drug stayed at 100%.

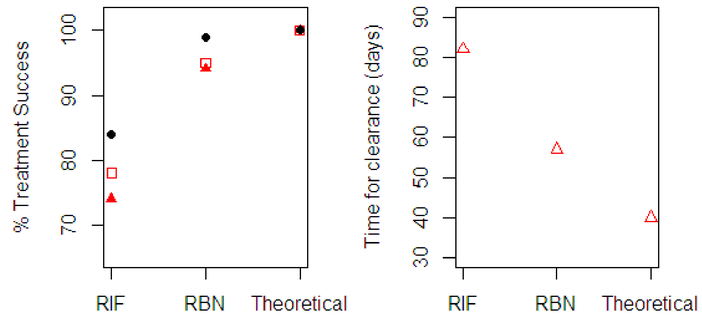

Figure 6: *Left: percent of model simulations in which total bacteria was under one at the end of therapy. Square: active bacteria. Triangle: total bacteria. Dots: total bacteria with perfect adherence. Right: Time for average clearance.*

Conclusion

- We matched our model against experimental data and can make predictions for future treatment options:
  - Rifabutin can increase treatment success, up to 99%, in 50 days
  - A new rifampin-like drug with a longer half-life, a short half-median effective dose, and a low dosage could increase treatment success, up to 100%, in 37 days.
  - Rifabutin and a slow decay drug could lessen the effect of patient non-adherence

Future Work

- Incorporating the immune response into the model
- Modeling drug resistant populations and TB-HIV co-infection

References

[1] M.L. Joloba, J.L. Johnson, A. Namale, A. Morrissey, A.E. Asseggai, R.D. Mugerwa, J.J. Ellner, and K.D. Eisenach. Quantitative sputum bacillary load during rifampin-containing short course chemotherapy in human immunodeficiency virus-infected and non-infected adults with pulmonary tuberculosis. *The International Journal of Tuberculosis and Lung Disease* 4, 6 (2000), 528–536.

[2] World Health Organization (WHO). WHO | how many TB cases have been successfully treated?

[3] Zhou, C., Chu, J., Liu, J., Gai Tobe, R., Gen, H., Wang, X., Zheng, W., and Xu, L. Adherence to tuberculosis treatment among migrant pulmonary tuberculosis patients in shandong, china: A quantitative survey study. *PLoS ONE* 7, 12 (Dec. 2012), e52334.

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