Predicting the Effectiveness of Novel Tuberculosis Treatment Regimens

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Background

- Tuberculosis (TB) is a prevalent disease, as it infects approximately one-third of the world's population
- Standard treatment of TB consists of four different drugs and lasts at least six months
- There is need for new treatment regimens, as the existing treatment plan is long and may inflict harsh side-effects—often leading to patient non-compliance and drug-resistant bacteria
- Human trials are not always ideal, as they are expensive and time consuming. Safety concerns and ethical issues may also arise when testing new drugs or treatment regimens on human subjects
- Mathematical models can be used as a supplement or alternative to human and animal trials in testing different treatment regimens.

Objective

- Implement a mathematical model that accurately simulates existing drug treatments of tuberculosis
- Use this mathematical model to simulate new treatment regimens and predict their effectiveness

Model Equations

$$\dot{B}_u = r_u B_u \left(1 - \frac{B_u}{N_b}\right) - \delta_u B_u - \mu_u B_u + \mu_p B_p - \sum_i f_{i,u} B_u$$

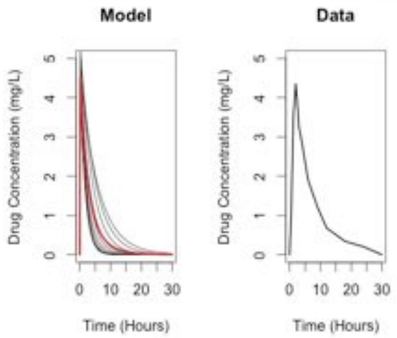
$$\dot{B}_p = r_p B_p \left(1 - \frac{B_p}{N_p}\right) - \delta_p B_p - \mu_p B_p + \mu_u B_u - \sum_i f_{i,p} B_p$$

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

$$C_i(t) = C_i(t) + C0_i, \qquad \text{every T hours}$$

$$f_{i,j} = \frac{k_{i,j} C_i^n}{C_i^n + C50_{i,j}^n}$$

Drug Model



A comparison between our model and experimental data of drug concentrations of rifampin (600 mg dose) in the pulmonary epithelial lining fluid.

Model Comparisons

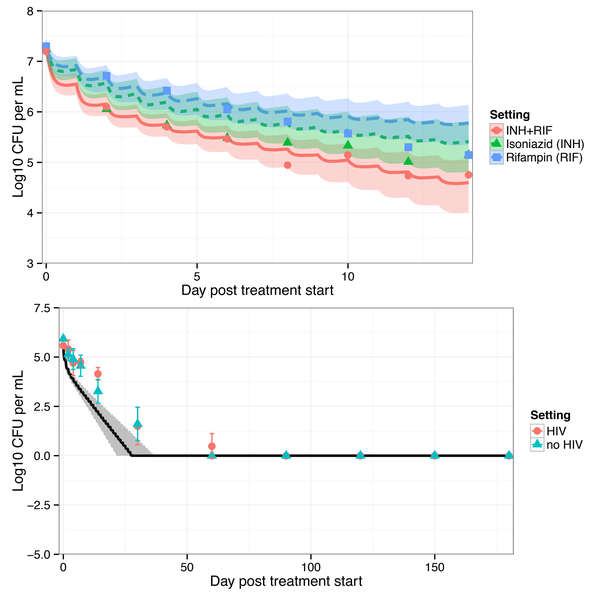
Time Series Comparison

Both Figures show the median and interquartile ranges of bacteria counts upon simulated treatment of 1000 patients.

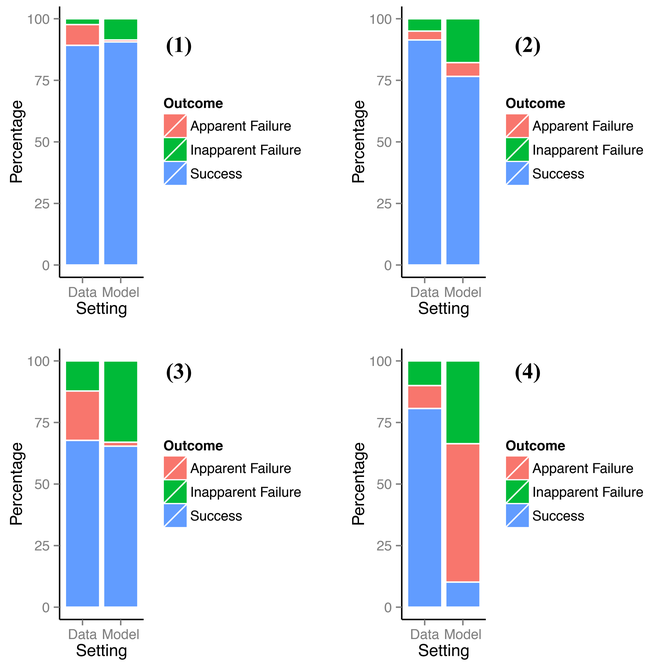
Top Figure:
Shows results over the first 14 days of treatments involving various drugs

Bottom Figure:
Shows results over six months of standard treatment involving:

- Two months of rifampin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) daily
- Four months of HR daily



Success Rate Comparison



All Figures show success rates of treatment of 500 simulated patients. Success occurs if less than 1 bacterium is present per kiloliter; apparent failure occurs if more than 100 bacteria are present per milliliter. Inapparent failure occurs when bacteria loads are between these two values. In this case, patients appear to be cured, but often are not.

(1) Eight weeks of HRZE followed by 18 weeks of HR daily

(2) Two months of HRZE daily, followed by six months of EH daily

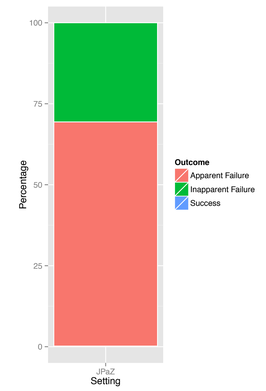
(3) Eight weeks of moxifloxacin (M) along with HRZ daily, followed by nine weeks of MHR daily

(4) Two months of HRZ followed by four months of HR taken twice weekly

Model Predictions

PaMZ Trials
The TB Alliance is conducting clinical trials on a treatment regimen consisting of pretomanid, moxifloxacin, and pyrazinamide, taken daily over eight weeks.

The left and right graphs show this regimen with a 200 mg dose and a 100 mg dose of pretomanid, respectively.



JPaZ Trials
Clinical trials are also in progress for a treatment plan including bedaquiline, pretomanid, and pyrazinamide.

Studies have only been done over 14 days of treatment. We run treatment for eight weeks with our model to predict long-term results of this regimen.

Conclusions and Future Work

- Newer treatment regimens (such as PaMZ) may be more effective overall in treating TB than standard regimens, and in a much shorter amount of time. Conversely, other treatments (such as JPaZ) may not perform as well as hoped.
- Our model should be worked on further to improve accuracy. Such improvements might include considering interactions between drugs, as well as modeling an immune response.
- New regimens should be thought of and then tested using our model

Acknowledgments

This research was funded by a National Science Foundation REU grant at the University of Georgia