Month 2 culture and duration as predictors of TB relapse

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M2C and duration as predictors of relapse

- A 2013 analysis of 24 trials published from 1973 to 1997 of 58 regimens studied in 7793 patients identified positive month 2 culture status using solid medium (M2C) and treatment duration as independent predictors of relapse.

- Predictions took the form: \( \text{logit}(\text{relapse}) = a + bx + cy \), where \( x = \text{logit}(\text{M2C}) \) and \( y = \text{log}(\text{duration}) \)

- The model was subsequently validated using independent data from 6 studies of 12 regimens involving 3907 patients.

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- REMox, OFLOTUB and RIFAQUIN:
  Results of the four 4-month arms were first predicted based on data from 5 phase 2 trials of 6 FQ regimens involving 443 patients. Relapse rates in all 8 arms of these 3 trials (3388 patients) were later predicted based on M2C and duration of each arm, at R² = .86.

- RELapse Treatment Shortening Trial:
  390 HIV-negative patients with non-cavitary disease at baseline and negative cultures at M2 were randomly assigned to 6 or 4 months total treatment. The study succeeded in showing low relapse rates in this population (1.6% and 7.0%, respectively), but failed by finding that duration was a predictor of relapse, contrary to the study hypothesis.

- Bangladesh regimen studies:
  MDR-TB patients were enrolled into 2 open label single arm cohort studies of a 12-month clofazimine-containing regimen in Niger and Cameroon. M2C positive proportions were 6% and 13%. 149 cured patients were followed for 1 year post cure. No relapses were found.

Wallis, PLoS One 2015
M2C and duration as predictors of relapse

Database characteristics

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<thead>
<tr>
<th>Total</th>
<th>Duration</th>
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<tbody>
<tr>
<td></td>
<td>3-5mo</td>
<td>6mo</td>
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<tr>
<td>Regimens</td>
<td>70</td>
<td>11</td>
</tr>
<tr>
<td>Subjects</td>
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<td>2824</td>
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Model parameters

<table>
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<tr>
<th></th>
<th>Estimate</th>
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<tbody>
<tr>
<td>Intercept</td>
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<td>0.478</td>
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<td>Ln duration</td>
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<td>Logit M2C+</td>
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<td>0.010</td>
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</table>

Online calculator at rswallis.com
M2C and duration as predictors of relapse

• The model is accurate ($R^2 > .9$) and generalizable (remaining accurate under previously untested conditions):
  • FQ results were predicted w/o FQ data
  • TBRU results were predicted w/o host data
  • MDR results were predicted w/o MDR or clofazimine data

• None of the studies in the training dataset and few in the validation dataset excluded recurrence due to reinfection
  • Presumably noise would be reduced and accuracy increased had they done so

• Data are insufficient to create a similar model using time to culture conversion in liquid medium, or one including baseline parameters
  • Collecting such data should be a research priority