Therapeutic threshold for rifampicin-resistant tuberculosis: a case report from Maputo, Mozambique – Detailed Methodology

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Layman's summary

Intuitively, it makes sense that the probability of disease of patients with given clinical profiles can be estimated based on each of their clinical indicators (e.g. symptoms, demographics, test results) that are potentially associated with either having the disease (inclusion) or not having the disease (exclusion).

Generally speaking, a prior probability and observed data can be combined into a posterior probability using Bayes' rule. In clinical decision-making, the most straightforward application involves multiplying prior odds of disease with the likelihood ratio of a clinical indicator to obtain the posterior odds of disease. The ingredients are therefore the odds of disease, which is uniquely defined by its corresponding probability through a closed form formula, and the likelihood ratio of a clinical indicator that can be readily estimated or approximated from either observed data or test characteristics such as sensitivity and specificity.

In our case study, we aim to estimate the probability of rifampicin-resistant tuberculosis (RR-TB) in a patient with confirmed tuberculosis. When such patients present, their baseline risk (probability) of RR-TB would be the (most accurate estimate of) RR-TB prevalence in the relevant setting: here the most recent estimate of the prevalence of RR-TB in Mozambique in someone with confirmed TB.

Following this procedure, relevant clinical indicators linked to RR-TB can be chained one after another to obtain new updated estimates for the probability of RR-TB for a patient with a specific clinical profile.

In a first step, we update the prevalence with the HIV status of the patient to obtain the probability of RR-TB of a person with confirmed TB who is also HIV positive. This posterior probability can then be used as a prior probability when we consider the next relevant clinical indicator.

In subsequent steps, we update the probability to include that our patient had treatment failure and later also re-treatment failure. Since these elements are all linked to an increased probability of RR-TB, they are said to be including or confirming for RR-TB.

In the last step, we consider the result from the Xpert rifampicin (RIF) drug susceptibility test (DST). The posterior probability of RR-TB for an HIV positive patient in Mozambique who had retreatment failure can now be called a pre-test probability as this is was the best estimate of the probability of RR-TB at the moment that the test was performed. Using the same methodology as before, we obtain the posterior probability after considering the likelihood ratio linked to the test result. This can also be called the post-test probability and is the final estimate of the probability of RR-TB of a patient with these characteristics.

In summary, the probability of RR-TB can be estimated by starting from the prevalence in the relevant population and updating it step by step with the strength of each of the clinical arguments.

The exact step-by-step calculations, and how we simulated the uncertainty intervals is detailed below.

Technical summary

Define Y as the outcome variable, here RR-TB, and $\bar{Y}$ as "not Y", i.e. RS-TB. Similarly denote X as the presence of a clinical indicator, e.g. "treatment failure" or "HIV positive", and $\bar{X}$ as "not X", the absence of this indicator.
The following formulas are the definition of the odds and likelihood ratios (LR):

$$odds(Y) = \frac{P(Y)}{P(\bar{Y})} = \frac{P(Y)}{1 - P(Y)}$$

$$LR(X|Y) = \frac{P(X|Y)}{P(X|\bar{Y})}$$

It can be directly proven by applying the classical Bayes' rule in both numerator and denominator of the odds, that a posterior odds is the product of the prior odds and likelihood ratio.

$$odds(Y|X) = \frac{P(Y|X)}{P(\bar{Y}|X)} = \frac{P(X|Y) * P(Y)/P(X)}{P(X|\bar{Y}) * P(\bar{Y})/P(X)} = \frac{P(X|Y)}{P(X|\bar{Y})} * \frac{P(Y)}{P(\bar{Y})} = LR(X|Y) * odds(Y)$$

Hence, an estimate of the posterior odds can be directly calculated when both the prior odds and likelihood ratio can be estimated.

In some cases, the likelihood ratio is not available in the literature and only an odds ratio can be used. Given the formula of the odds ratio, it can be easily proven that

$$OR(Y|X) = \frac{odds(Y|X)}{odds(Y|\bar{X})} = \frac{P(Y|X)\,P(\bar{Y}|\bar{X})}{P(\bar{Y}|X)\,P(Y|\bar{X})} = \frac{P(X|Y)\,P(\bar{X}|\bar{Y})}{P(X|\bar{Y})\,P(\bar{X}|Y)} = \frac{LR(X|Y)}{LR(\bar{X}|Y)}$$

$$LR(X|Y) = OR(Y|X) * LR(\bar{X}|Y)$$

As such, when an estimate for the likelihood ratio of the absence of the indicator can be estimated, a number that is typically closer to 1 and hence less variable, we can use the odds ratio with this correction applied instead.

Additionally, the likelihood ratio and odds ratio do uniquely define each other for a given prevalence of the indicator, albeit not through a straightforward closed-form formula.

In summary, we use the following formula to update the prior probability of RR-TB step by step.

$$odds(Y|X) = LR(X|Y) * odds(Y)$$

When the likelihood ratio cannot be directly found in the literature, we use the odds ratio instead with the offset as defined above.

Finally, resistance can also be acquired during treatment. The probability of acquired resistance as estimated from the literature can be directly added as the proportion of additional resistance if there

would have been no initial resistance. If we define Y^A as acquired resistance, and $Y^{\bar{A}}$ consequently resistance, but not acquired during treatment (initial resistance), with X treatment failure, then the formula for overall resistance after treatment failure becomes:

$$P(Y|X) = P(Y^{\bar{A}}|X) + \left(1 - P(Y^{\bar{A}}|X)\right) * P(Y^A|X)$$

Uncertainty intervals

The uncertainty around the probability of RR-TB is simulated. All calculations (detailed in the next section) are repeated 1000 times with the point estimate each time replaced by a random draw from the underlying distribution of the relevant measure.

Reported confidence intervals are typically calculated from parametric distributions: log-odds and log-LR are assumed to be normally distributed, while for probabilities, Clopper-Pearson confidence intervals and their associated underlying distribution (F-distribution) are used or assumed. By matching reported confidence limits to the respective quantiles, we are able to determine the sampling distribution around the point estimate.

Thus, after each step, we obtain 1000 draws from the distribution of the relevant parameter (i.e. the odds or probability of RR-TB). We define our 95% uncertainty interval as the range between the 2.5% and 97.5% quantile of these draws.

Step by step calculations

Step 0 – Start

Expanding notation for layman readers, we start from a general P(RRTB), the prevalence of RR-TB in the relevant setting. This is in essence P(RRTB|Mozambique), which we estimate from the most recent global TB report. Of note, this estimate is subject to uncertainty from the WHO models to estimate the prevalence. The reported point estimate is **3.7%**, with a confidence interval **[2.5%;5.2%]**.

We decided to not include age because (a) the patient was 40 years old, which is the cut-off point in a meta-analysis that studied risk factors for RR-TB and (b) the point estimate for the odds ratio was close to 1, indicating that any association with age was negligible at best.

Any symptoms linked to TB were ignored as well as the patient was assumed to be a confirmed TB case (i.e. P(TB)=1). If the TB diagnosis would have been in doubt, any future results would have to be multiplied with P(TB).

Since we had no reliable information on possible contacts with an RR-TB case, this was not included either.

Step 1 – HIV status

The patient was HIV positive when diagnosed with TB. The reported odds ratio for RRTB HIV vs. no HIV was 1.49 with 95% confidence interval [0.73;3.06]. For an HIV prevalence of 36% in TB positive patients, this translates to a positive likelihood ratio of 1.27 and a negative likelihood ratio of 0.85 (1.49*0.85=1.27).

After step 1, we obtain:

$$\begin{aligned} odds(RRTB|HIV, Moz) &= LR(HIV|RRTB, Moz) * odds(RRTB|Moz) \\ &= (1.49 * 0.85) * \frac{0.037}{0.963} = 0.0487 \end{aligned}$$

While not formally needed for the next step, we can transform the odds to a probability with the usual formula and format it as a percentage:

$$P(RRTB|HIV, Moz) = \frac{odds(RRTB|HIV, Moz)}{1 + odds(RRTB|HIV, Moz)} = \mathbf{4.64}\%$$

For simulation purposes, logit(RRTB|Moz) (i.e. the log-odds) was simulated from a normal distribution with mean log(0.037/0.963) and standard deviation [log(0.052/0.948)-log(0.025/0.975)]/(2*1.96), derived from the formula for the (width of) the confidence interval.

The likelihood ratio also changes with changing odds ratio and was estimated accordingly (no closed formula as detailed in the previous section).

The estimated point estimate through simulation (median) is **4.69%**, closely approximating the direct point estimate, with 95% uncertainty interval: **[2.91%;7.48%]**.

Step 2 – Treatment failure

The patient had treatment failure on a first-line regimen. We followed the exact same reasoning as step 1. The odds ratio for initial RRTB (noted here as iRRTB) and treatment failure is 7.24 (95% CI [4.06 – 12.89]) and assumed to be the same in HIV patients as in non-HIV positive TB patients. The associated positive likelihood ratio was estimated to be around 5.1, with a negative likelihood ratio of 0.7 (7.24*0.7=5.07).

After step 2, we obtain:

$$\begin{aligned} odds(iRRTB|TrFail, HIV, Moz) &= LR(TrFail|iRRTB, HIV, Moz) * odds(iRRTB|HIV, Moz) \\ &= (7.24 * 0.7) * 0.0487 = 0.2466 \end{aligned}$$

with probability formatted as a percentage:

$$P(iRRTB|TrFail, HIV, Moz) = \frac{odds(iRRTB|TrFail, HIV, Moz)}{1 + odds(iRRTB|TrFail, HIV, Moz)} = \mathbf{19.78}\%$$

The simulation, following the same structure as in step 1, resulted in a median of **20.30%** with 95% uncertainty interval: **[10.04%;34.98%]**.

This OR, and consequently also the final result, is based on having initial RR-TB, i.e. the resistance was present before starting the treatment. Patients may also acquire resistance during their treatment (noted here as aRRTB). The probability of acquiring resistance during treatment failure is estimated to be 0.286 (95% CI: [0.084;0.581]). Since resistance can only be acquired when the treatment fails and no initial resistance was present, the probability of RRTB after treatment failure can be estimated as:

$$\begin{aligned} P(RRTB|TrFail, \dots) &= P(iRRTB|TrFail, \dots) + P(aRRTB|TrFail, \dots) * \big(1 - P(iRRTB|TrFail, \dots)\big) \\ &= 0.1978 + 0.286 * (1 - 0.1978) = 0.4270 \end{aligned}$$

Hence, the total probability of RRTB after treatment failure is estimated to be **42.70%**. The simulation produced a median estimate of **44.73%** with a wide 95% uncertainty interval: **[24.73%;68.40%]**, mainly due to considerable uncertainty around acquired resistance. Since this involved a probability, the Clopper-Pearson formula and its associated distribution was used for simulation as detailed in the previous section.

Step 1+2 alternative – HIV and Previous TB

In this step, we could also have chosen to instead start from the estimate of having RR-TB for someone with a history of TB from the Global TB report which is estimated to be 20% (95% CI [5.2%-40%]). Assuming the same likelihood ratio for HIV with respect to RR-TB in someone with a history of TB compared to an initial case, we'd get

$$\begin{aligned} odds(RRTB|TBhist, HIV, Moz) &= LR(HIV|RRTB, TBhist, Moz) * odds(iRRTB|HIV, TBhist, Moz) \\ &= (1.49 * 0.85) * \frac{0.20}{0.80} = 0.3166 \end{aligned}$$

The associated probability would be **24.05%**. This is as expected higher than the probability of having initial RR-TB after treatment failure, but lower than the overall probability of having RR-TB after treatment failure since a history of TB is a combination of relapses and reinfections. We assumed treatment failure rather than a history of TB for our patient and as such did not further consider this alternative starting point.

Step 3 – Re-treatment failure

For re-treatment failure, we have a direct estimate of the likelihood ratio of 19.1 for initial resistance (before re-treatment, but after first treatment), with 95% CI: [15.2; 24.1].

Following the same procedure for initial and acquired RR-TB as in step 2, we get:

$$odds(iRRTB|ReTrFail, \dots) = LR(ReTrFail|iRRTB, \dots) * odds(iRRTB| \dots)$$
$$= 19.1 * \frac{0.4270}{0.5730} = 14.24$$

with probability formatted as a percentage:

$$P(iRRTB|ReTrFail, \dots) = \frac{odds(iRRTB|ReTrFail, \dots)}{1 + odds(iRRTB|ReTrFail, \dots)} = \mathbf{93.44}\%$$

The simulation resulted in a median of **93.91%** with 95% uncertainty interval: **[90.67%;98.44%]**. A similar approach as in step 1 was used, with the formula for a direct likelihood ratio rather than the odds ratio.

Adding the probability of acquiring resistance during re-treatment failure, the probability of RRTB after treatment failure can be estimated as:

$$P(RRTB|ReTrFail, \dots) = P(iRRTB|ReTrFail, \dots) + P(aRRTB|ReTrFail, \dots) * \big(1 - P(iRRTB|ReTrFail, \dots)\big)$$
$$= 0.9344 + 0.319 * (1 - 0.9344) = 0.9553$$

Hence, the total probability of RRTB after re-treatment failure is **95.53%**.
The simulation, following the identical procedure as in step 2, resulted in a median of **95.87%** with 95% uncertainty interval: **[90.67%;98.44%]**.

Step 4 – Xpert MTB+/RIF-

The patient was then tested for RIF resistance. Given the previous result, clinicians likely assumed that the test would confirm their assumption of likely resistance. However, the test was unexpectedly negative for RIF resistance, a strong excluding argument for RR-TB.

Using the most recent sensitivity and specificity estimates for DST with Xpert, we have P(RIF+|RR)=96% (95% CI [94%;97%], sensitivity) and P(RIF-|RS)=98% (95% CI [98%;99%], specificity). This translates to a negative likelihood ratio estimate of 0.0408, or an excluding power of approximately 25.

Following the same procedure as in step 3, we get:

$$odds(RRTB|RIF-, \dots) = LR(RIF - |RRTB, \dots) * odds(RRTB| \dots)$$
$$= \frac{0.04}{0.98} * \frac{0.9553}{0.0447} = 0.8724$$

The final probability, formatted as a percentage:

$$P(RRTB|RIF-, ReTrFail, TrFail, HIV, Moz) = \frac{odds(RRTB|RIF-, \dots)}{1 + odds(RRTB|RIF-, \dots)} = \mathbf{46.59}\%$$

The simulation resulted in a median of **48.80%** with 95% uncertainty interval: **[26.47%;73.74%]**.