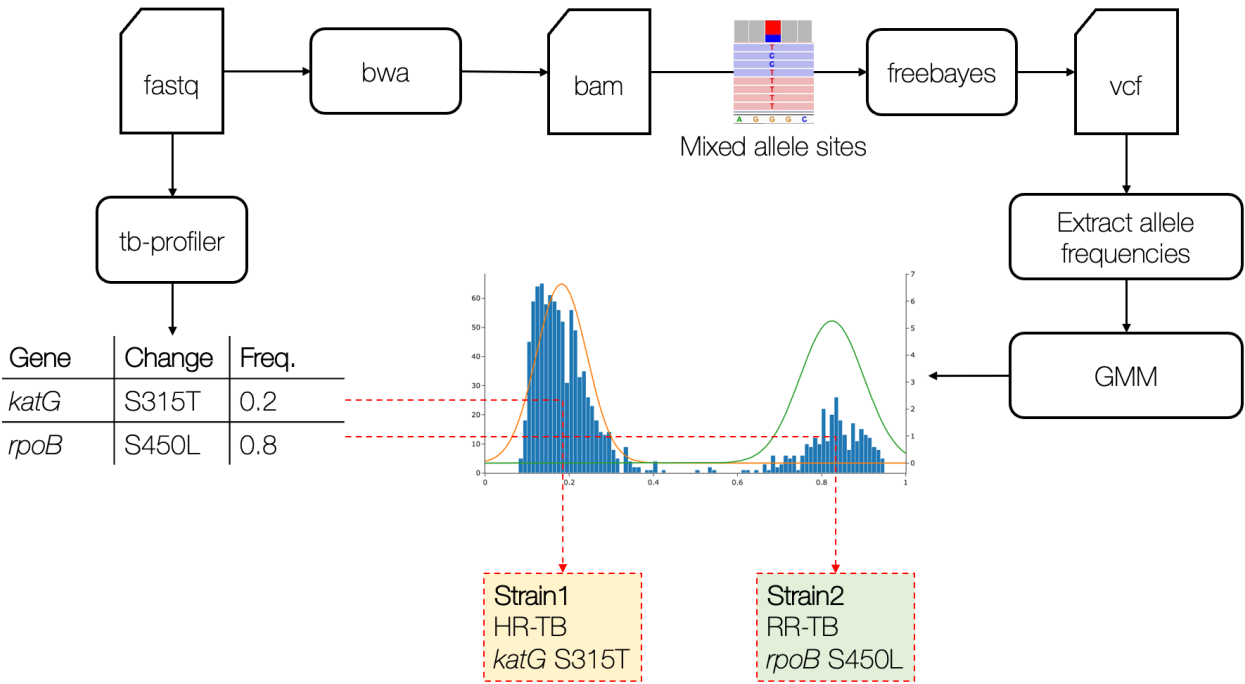


SUPPLEMENTARY INFORMATION

S1 Figure

The approach: GMM Gaussian Mixture model



**S1 Table****Common combinations of sub-lineages in the MSIs (n=207/531)**

| <b>(Sub-)lineage</b> | <b>(Sub-)Lineage</b> | <b>Count</b> |
|----------------------|----------------------|--------------|
| L4                   | L2.2.1               | 28           |
| L4.4.1.1             | L2.2.1               | 17           |
| L4.3.3               | L2.2.1               | 16           |
| L2.2.1               | L1.1.1.1             | 16           |
| L3                   | L2.2.1               | 14           |
| L4                   | L3                   | 12           |
| L4.5                 | L2.2.1               | 9            |
| L2.2.1               | L1.1.2               | 9            |
| L4.3.3               | L4.1.2.1             | 8            |
| L4.1.2.1             | L2.2.1               | 7            |
| L4.8                 | L2.2.1               | 7            |
| L4                   | L1.2.2.2             | 6            |
| L4.3.3               | L3                   | 6            |
| L2.2.2               | L2.2.1               | 6            |
| L1.2.2.2             | L1.1.2               | 6            |
| L4.5                 | L4.4.2               | 5            |
| L4                   | L3.1.1               | 5            |
| L4.1.2.1             | L4.1.1               | 5            |
| L2.2.1               | L1.1.1               | 5            |
| L3                   | L1.1.2               | 5            |
| L4.4.2               | L2.2.1               | 5            |
| L4.8                 | L4.3.3               | 5            |
| L4.2.1               | L2.2.1               | 5            |

S2 Table

The drug resistance profiles of the *M. tuberculosis* isolate with putative evidence of mixed strain infections (n=531)

| Count         | Sensitive   | MDR+        | HR-TB      | RR-TB     | Other*                                                                                                           |
|---------------|-------------|-------------|------------|-----------|------------------------------------------------------------------------------------------------------------------|
| 220           | X           |             |            |           |                                                                                                                  |
| 74            | X           | X           |            |           |                                                                                                                  |
| 50            | X           |             |            |           | ethambutol, ethionamide, kanamycin, cycloserine, ofloxacin, para-aminosalicylic acid, pyrazinamide, streptomycin |
| 44            | X           |             | X          |           |                                                                                                                  |
| 41            |             | X           |            |           |                                                                                                                  |
| 20            | X           |             |            | X         |                                                                                                                  |
| 19            |             | X           | X          |           |                                                                                                                  |
| 15            |             | X           |            |           | ethambutol, ethionamide, kanamycin, ofloxacin, para-aminosalicylic acid, pyrazinamide, streptomycin              |
| 11            |             |             | X          |           | ethionamide, kanamycin, ofloxacin, para-aminosalicylic acid, streptomycin                                        |
| 8             |             |             | X          | X         |                                                                                                                  |
| 7             |             | X           |            | X         |                                                                                                                  |
| 7             | X           |             |            |           |                                                                                                                  |
| 4             |             |             |            | X         | ethambutol, ofloxacin, pyrazinamide, streptomycin                                                                |
| 4             |             |             |            |           | capreomycin, ethambutol, ofloxacin, ethionamide, streptomycin                                                    |
| 3             |             |             | X          | X         |                                                                                                                  |
| 2             | X           | X           | X          |           |                                                                                                                  |
| 1             | X           | X           | X          |           | ethambutol, kanamycin, ofloxacin, streptomycin, ethambutol                                                       |
| 1             | X           |             | X          | X         |                                                                                                                  |
| Overall N (%) | 451 (85.0%) | 145 (27.3%) | 90 (16.9%) | 31 (5.9%) | 76 (14.3%)                                                                                                       |

HR-TB: isoniazid mono-resistance. RR-TB: Rifampicin resistance; MDR-TB+: Multidrug resistance and above, including extensively drug-resistant; Other: drug resistances specified in the column found in the contributing lineage of the mixture.

### S3 Table

#### Performance of the GMM and alternative approaches on 48 mixtures of Malawi *M. tuberculosis* DNA

| Strain mix ratio* | N  | GMM<br>MSE | TB-Profiler<br>MSE | Quant-TB<br>MSE |
|-------------------|----|------------|--------------------|-----------------|
| 30:70             | 12 | 0.0175     | 0.0158             | 0.0078          |
| 10:90             | 12 | 0.0046     | 0.0044             | 0.0074          |
| 5:95              | 12 | 0.0031     | 0.0024             | 0.0282          |
| 0:100             | 12 | 0.0000     | 0.0000             | 0.0367          |
| Overall           | 48 | 0.0063     | 0.0057             | 0.0200          |

\* Minor: Major; MSE mean squared error

**S4 Table**

**Performance of the GMM and alternative methods on 240 artificial *in-silico* mixtures with drug resistance (DR) mutations**

| Strain mix ratio* | N   | GMM MSE | GMM DR Accuracy | TB-Profiler MSE | Quant-TB MSE |
|-------------------|-----|---------|-----------------|-----------------|--------------|
| 5:95              | 24  | 0.0208  | 0.9229          | 0.0044          | 0.0015       |
| 10:90             | 24  | 0.0155  | 0.9554          | 0.0062          | 0.0047       |
| 15:85             | 24  | 0.0146  | 0.8919          | 0.0086          | 0.0067       |
| 20:80             | 24  | 0.0168  | 0.8979          | 0.0104          | 0.0091       |
| 25:75             | 24  | 0.0157  | 0.9239          | 0.0105          | 0.0150       |
| 30:70             | 24  | 0.0128  | 0.9279          | 0.0090          | 0.0149       |
| 35:65             | 24  | 0.0088  | 0.9270          | 0.0065          | 0.0140       |
| 40:60             | 24  | 0.0044  | 0.9662          | 0.0102          | 0.0129       |
| 45:55             | 24  | 0.0035  | 0.8878          | 0.0182          | 0.0171       |
| 50:50             | 24  | 0.0076  | 0.9286          | 0.0044          | 0.0264       |
| Overall           | 240 | 0.0121  | 0.9230          | 0.0088          | 0.0122       |

\* Minor: Major; MSE mean squared error