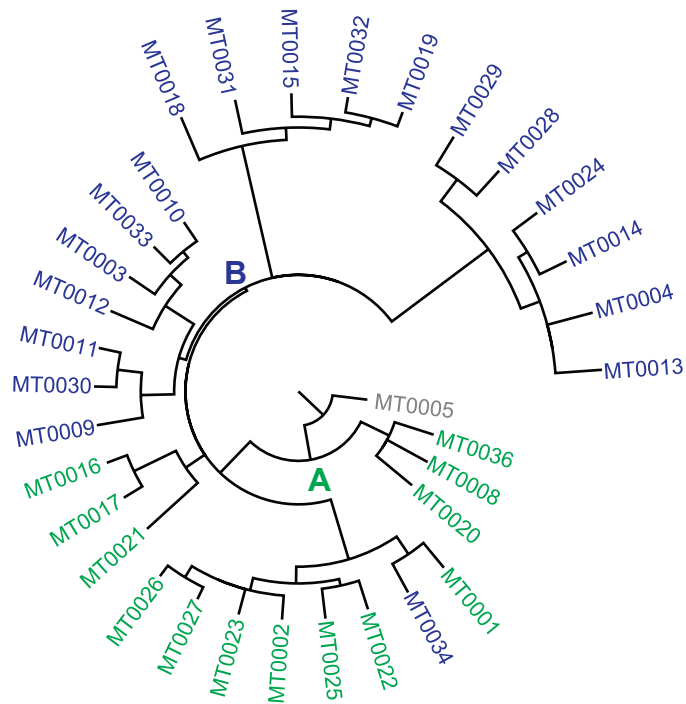
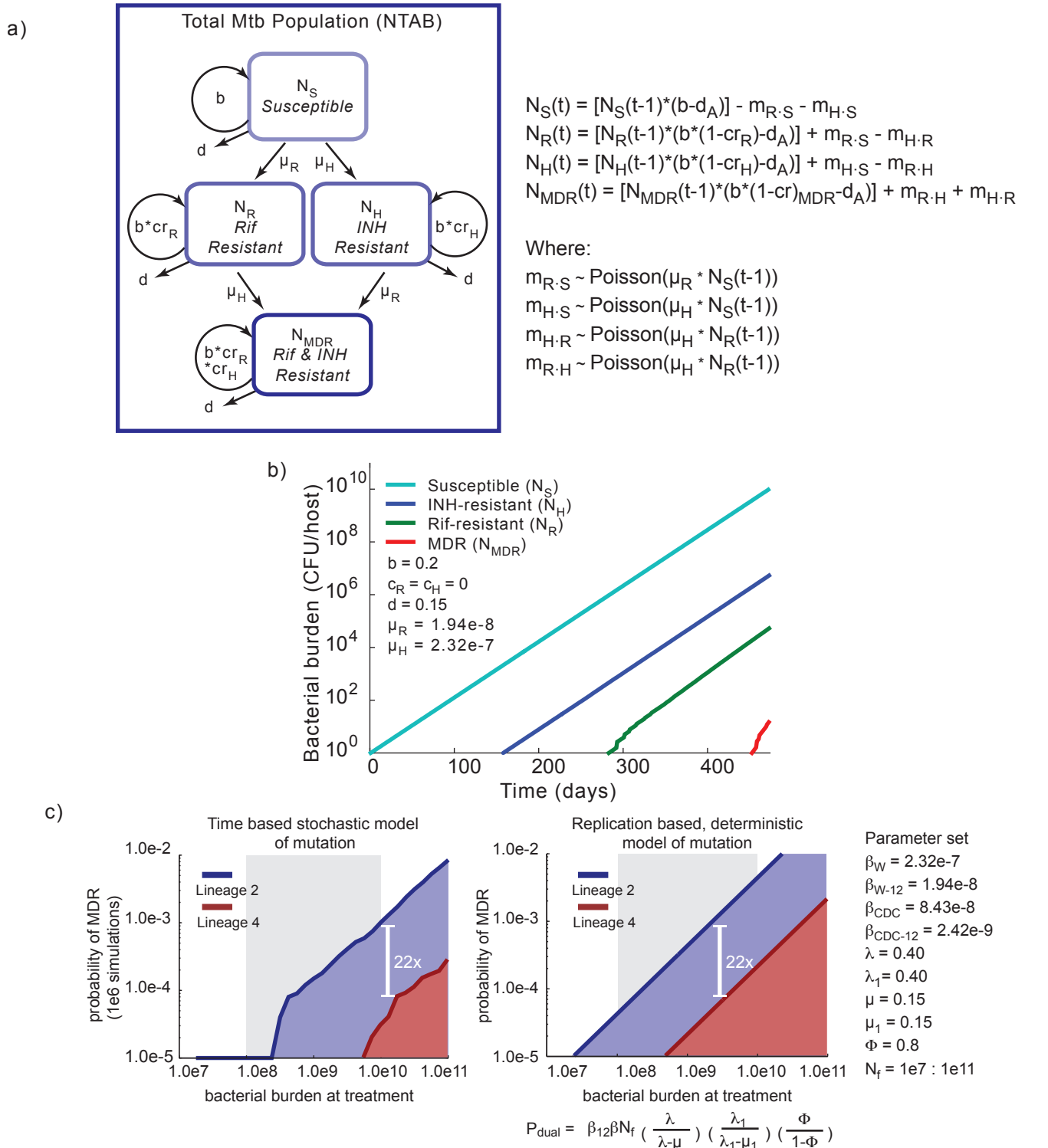


Supplementary Figure 1



Supplementary Figure 1 Phylogeny of isolates from human transmission chain. A possible phylogeny of isolates from a human transmission chain in British Columbia, Canada. The phylogeny was reconstructed from concatenated SNPs, excluding SNPs in PE_PGRS, PPE, and transposable elements (consistent with our previous analysis) using BEAST, v.1.7.2 to estimate the mutation rate under neutral conditions. The previously defined groupings are noted. Group A is shown in green, group B is shown in blue, and the historical isolate, MT0005 is shown in grey.

Supplementary Figure 2



Supplementary Figure 2 A stochastic simulation model of multidrug resistance. (a) The structure and equations of the model for a single patient are displayed. The model was run multiple times in accordance with the parameter values displayed in Supplementary Table 5. **(b)** The results of the model for a single patient in whom multidrug resistance evolved. **(c)** A comparison of our model (left) and a model of multidrug resistance based on mutation occurring every generation, with allowance for mutation accrual before cell death (Colijn et al, 2010). Expected bacterial burden during treatment is shown by the grey background.

Supplementary Table 1 Fluctuation analysis data

Strain	Lineage	Drug ($\mu\text{g}/\mu\text{L}$)	MIC Rif INH ($\mu\text{g}/\mu\text{L}$)	Total cultures	m^a	Cell count ^b	Mutation rate ^c	95% Confidence Interval
CDC-1551	Euro-American	Rif 2	<0.01531 <0.00766	20	2.153	8.90e8	2.42e-9	1.14-3.82e-9
Erdman	Euro-American	Rif 2	<0.01531 <0.00766	20	2.274	8.64e8	2.63e-9	1.26-4.13e-9
H37Rv	Euro-American	Rif 2	<0.01531 <0.00766	20	4.337	8.73e8	4.97e-9	2.94-7.08e-9
X005581	Euro-American	Rif 2	<0.01531 <0.00766	20	5.830	7.70e8	7.57e-9	4.09-8.58e-9
X000630	Euro-American	Rif 2	<0.01531 <0.00766	20	4.815	8.50e8	5.67e-9	5.2-11.9e-9
HN878	East Asian	Rif 2	<0.01531 <0.00766	20	15.809	1.17e9	1.35e-8	1.10-1.61e-8
X005632	East Asian	Rif 2	<0.01531 <0.00766	20	7.898	8.80e7	8.97e-8	6.34-11.7e-8
X005631	East Asian	Rif 2	<0.01531 <0.00766	20	3.225	1.37e8	2.36e-8	1.26-3.52e-8
X005621	East Asian	Rif 2	<0.01531 <0.00766	20	5.523	2.04e8	2.71e-8	1.73-3.72e-8
CDC-1551	Euro-American	Rif 0.5	<0.01531 <0.00766	20	5.100	6.08e8	8.40e-9	5.24- 11.7e-9
CDC-1551	Euro-American	Rif 2	<0.01531 <0.00766	20	2.919	6.08e8	4.81e-9	2.48-7.28e-9
CDC-1551	Euro-American	Rif 5	<0.01531 <0.00766	17	3.171	6.08e8	5.22e-9	2.73-7.88e-9
HN878	East Asian	Rif 0.5	<0.01531 <0.00766	16	16.998	9.38e8	1.81e-8	1.49-2.14e-8
HN878	East Asian	Rif 2	<0.01531 <0.00766	19	18.223	9.38e8	1.94e-8	1.61-2.28e-8
HN878	East Asian	Rif 5	<0.01531 <0.00766	20	9.311	9.38e8	9.39e-9	7.29-11.3e-9
CDC-1551	Euro-American	INH 1	<0.01531 <0.00766	20	145.3	1.72e9	8.43e-08	8.14-8.72e-8
HN878	East Asian	INH 1	<0.01531 <0.00766	18	93.36	4.03e8	2.32e-7	2.19-2.43e-7
CDC-1551	Euro-American	ETH 5	<0.01531 <0.00766	20	19.60	3.93e8	4.98e-8	4.18-5.80e-8
HN878	East Asian	ETH 5	<0.01531 <0.00766	20	20.02	1.60e8	1.25e-7	1.05-1.45e-7

^am represents the estimated number of mutations per culture as determined by the MSS method. ^b Cell count is the average number of cells per culture plated on antibiotic. Dividing m by cell count gives the estimated mutation rate.

Supplementary Table 2 Differences in AIC_C

Strain	Rifampicin (ug/mL)	AIC_C(LD) - AIC_C (TP)	AIC_C(LD) - AIC_C(Poiss)	AIC_C(TP) - AIC_C(Poiss)
CDC-1551	0.5	-2.1711	-221.7147	-219.5436
CDC-1551	2	-3.1706	-101.3108	-98.1402
CDC-1551	5	-1.8248	-34.8242	-32.9994
HN878	0.5	-2.0739	-248.8711	-246.7972
HN878	2	-1.7125	-632.029	-630.3165
HN878	5	-0.608	-118.6105	-118.0026

Supplementary Table 3 Target size

<i>E.coli</i> RpoB Coord. (amino acid)	Mtb RpoB Coord. (amino acid)	Mtb <i>rpoB</i> coord. (nucleotide)	Number of isolates CDC -1551			Number of isolates HN878		
			<i>Drug Concentration (µg/mL)</i>					
			0.5	2	5	0.5	2	5
Q513E	Q438E	C1312G	-	-	-	2	1	-
Q513L	Q438L	A1313T	-	-	-	2	-	-
D516V	D441V	A1322T	1	-	-	3	-	-
N519K	N444K	C1332G	-	-	-	1	-	-
S522L	S447L	C1340T	7	7	-	4	13	2
S522W	S447W	C1340G	4	2	5	4	3	3
H526D	H451D	C1351G	14	9	4	9	3	7
H526Y	H451Y	C1351T	10	12	12	10	15	14
H526R	H451R	A1352G	7	7	13	15	10	14
H526P	H451P	A1352C**	1	4	5	1	3	5
H526L	H451L	A1352T	2	-	-	1	-	-
S531L	S456L	C1367T	11	8	5	7	16	18
S531W	S456W	C1367G	1	2	1	1	2	-
Total Target Size			10	8	7	13	9	7

** A1352C represents both single mutations found at this single site (quantity per strain : 1,2,-,1,1,1 respectively), as well as three clustered mutations: C1350G, A1352C, A1354C (quantity per strain: -, 2,5,-,2,4). These three mutations were found together, and the first of the three is a silent mutation.

Supplementary Table 4 Per base mutation rate from fluctuation analysis data on multiple concentrations of rifampicin

Drug Conc. (µg/mL)	Strain	Mutation Rate (mut./bp/gen.)	95% CI	Wilcoxon Rank Sum p-value
0.5	CDC1551	8.40e-10	5.24e-10 – 1.17e-9	4.29e-06
	HN878	1.39e-09	1.14e-9 - 1.65e-9	
2	CDC1551	6.01e-10	3.10e-10 – 9.10e-10	1.85e-05
	HN878	2.16e-09	1.79e-9 – 2.53e-9	
5	CDC1551	7.46e-10	3.91e-10 – 1.13e-9	3.82e-04
	HN878	1.42e-09	1.04e-9 – 1.80e-9	

Supplementary Table 5 Per base pair per day mutation rate estimates for isolates *in vivo* and *in vitro*

Sample	Mutations (m)	Number of genomes	Average time per genome (days)	Mutation rate	95% CI
Human isolates*	n/a	32	n/a	2.21e-10	1.90 – 2.52 e-10
Active Disease, cynomolgus macaque**	4	15	261.85	4.45e-10	4.01 - 4.88 e-10
Latent infection, cynomolgus macaque**	3	8	293.52	2.55e-10	6.59 – 93.3 e-10
Reactivated Disease, cynomolgus macaque**	7	10	488.69	3.19e-10	1.44 - 7.38 e-10
All disease states, cynomolgus macaque**	14	33	338.31	3.14e-10	1.71 - 5.26 e-10
<i>In vitro</i>, Erdman**	10	n/a	n/a	3.16e-10	1.51 - 4.95 e-10

* Estimated using BEAST v1.7.2

** Previously published, see reference (6).

Supplementary Table 6 Parameter values for stochastic simulation mathematical model of multidrug resistance

Variable	Descriptor	Figure 7a	Figure 7b	Figure 7c
N_S(t)	Susceptible bacterial population size at time (t)	Variable	Variable	Variable
N_R(t)	Rifampicin Resistant bacterial population size at time (t)	Variable	Variable	Variable
N_H(t)	Isoniazid Resistant bacterial population size at time (t)	Variable	Variable	Variable
N_{MDR}(t)	Multidrug resistant bacterial population size at time (t)	Variable	Variable	Variable
b	Bacterial growth rate, replications per day	0.40	0.20 : 1.10, increments of 0.10	0.40
d_A	Bacterial death rate	0.15	0.15	0.15
μ_{R-CDC}	Rifampicin resistance rate, CDC-1551	2.42e-9	2.42e-9	2.42e-9
μ_{H-CDC}	Isoniazid resistance rate, CDC-1551	2.32e-7	2.32e-7	2.32e-7
μ_{R-W}	Rifampicin resistance rate, HN878	1.94e-8	1.94e-8	1.94e-8
μ_{H-W}	Isoniazid resistance rate, HN878	2.32e-7	2.32e-7	2.32e-7
cr_H	Fitness cost of resistance, isoniazid resistance	0	0	0 : 0.9, increments of 0.10
cr_R	Fitness cost of resistance, rifampicin	0	0	0 : 0.9, increments of 0.10
cr_{MDR}	Fitness cost of resistance, multidrug resistance	cr _H *cr _R	cr _H *cr _R	cr _H *cr _R
Number of runs	Number of simulated patients	100,000 per strain	1,000,000 (100,000 per value of b, per strain)	1,000,000 (100,000 per value of cr, per strain)