Supplementary Table 1: Main ciprofloxacin resistance mutations in the target genes in *Neisseria gonorrhoeae* (1). Changes in the amino acid positions increase ciprofloxacin MICs against *N. gonorrhoeae*. The first letter (e.g. S) is the wildtype amino acid and the # (e.g. 91) is the amino acid position at which a change occurs.

Target	Resistance mutations/amino acid changes
GyrA	S91[±D95][1]
ParC	D86, S87, S88, E91

[1] The combination of S91 and D95 confers a greater level of resistance to ciprofloxacin (measured in terms of MIC) than either mutation alone (2).

Supplementary Text 1 – Microbiological Analysis of the gepotidacin phase II trial

Five baseline isolates in the phase II clinical trial had a gepotidacin MIC of 1 mg/L and were ciprofloxacin-resistant, compared to a modal gepotidacin MIC of 0.5 mg/L for ciprofloxacin-resistant isolates in a separate study, and an MIC of 32 mg/L for test-of-cure isolates from two of three treatment failures in the phase II clinical trial (3, 4). The ratio of the area under the free-drug concentration-time curve to the MIC (fAUC/MIC) was associated with microbiologic success in the trial. Success was 100% at fAUC/MICs of ≥48 and decreased to 63% for fAUC/MICs of ≤25. All 3 isolates from microbiological failures were ciprofloxacin-resistant, had a baseline gepotidacin MIC of 1 mg/L, and carried a ParC D86N mutation, a critical residue for gepotidacin binding. Test-of-cure isolates from two of the three treatment failures demonstrated resistance emergence to gepotidacin with MICs of ≥32mg/L and had an additional GyrA A92T mutation, also a critical residue for gepotidacin binding. Therefore, the ParC D86N (first step) and GyrA A92T (second step) mutations can be considered 'stepping-stone' mutations with respect to gepotidacin resistance.

Supplementary Table 2. All rates are per day. If more than one value is given, the whole range of values has been tested in different simulations. See Supplementary Excel workbook for parameter combinations used in individual simulations.

Model parameter [unit]	Values used in individual simulations	References
Infection rate parameter [per day]	5.56×10^{-8}, 1.67×10^{-8}, 6.02×10^{-8}, 2.28×10^{-7}, 2.29×10^{-7}	Fitted so that the equilibrium annual incidence rate in the absence of resistant strains was about 22,000 (total population $1.5\text{x}10^{6}$) (5)
Recovery rate f (inverse of duration of natural infection) [per day]	1/84, 1/160, 1/185, 1/240, 1/365	(6-12)
Treatment rate γ (inverse of time in days until patients first seek treatment) [per day]	1/3, 1/12, 1/13, 1/52	(9, 13, 14)
Cure rate gepotidacin, assuming double dose (inverse of treatment duration, i.e. time over MIC) [per day]	1.778 (=1/13.5h)	Information provided by GSK (derived from simulations of PK model published in (15, 16))
Cure rate ciprofloxacin, assuming single dose (inverse of treatment duration) [per day]	6 (=1/4h)	(17)
Proportion of patients that return for 2nd round treatment p	1, 0.8, 0.6, 0.5	Assumptions (1 means all patients return for 2nd round treatment, but because this perfect scenario is unlikely, we tested several lower values)
Mutation rate without treatment σ_b [substitutions per nucleotide per day]	3.12×10^{-9}, 2.45×10^{-8}	(12, 18, 19)
Mutation rate with treatment σ_t [substitutions per nucleotide per day]	3.12×10^{-9}, 2.45×10^{-8}, 4.9×10^{-8}, 1.23×10^{-7}, 2.45×10^{-7}, 2.45×10^{-6}, 2.45×10^{-5}, 7.95×10^{-5}, 9.66×10^{-4}	Assumptions (based on mutation rates published for bacteria under antibiotic treatment: (20-28))
Point-of-care test usage [%]	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100	Assumptions (sensitivity analysis over the possible range of POCT uptake from 0-100%)
Total simulated population	1.5×10^{6}	(5)
Initial number of infected individuals/equilibrium incidence rate	22,000	(5)
Initial prevalence of ParC D86N [%]	0, 0.06, 0.18, 0.462, 0.669, 1.5, 2, 2.9, 3, 5.9, 6.5, 8.6, 13, 19.3, 38.6	Assumptions based on multiplying published frequencies of ParC D86N mutations in quinolone-resistant strains with published levels of

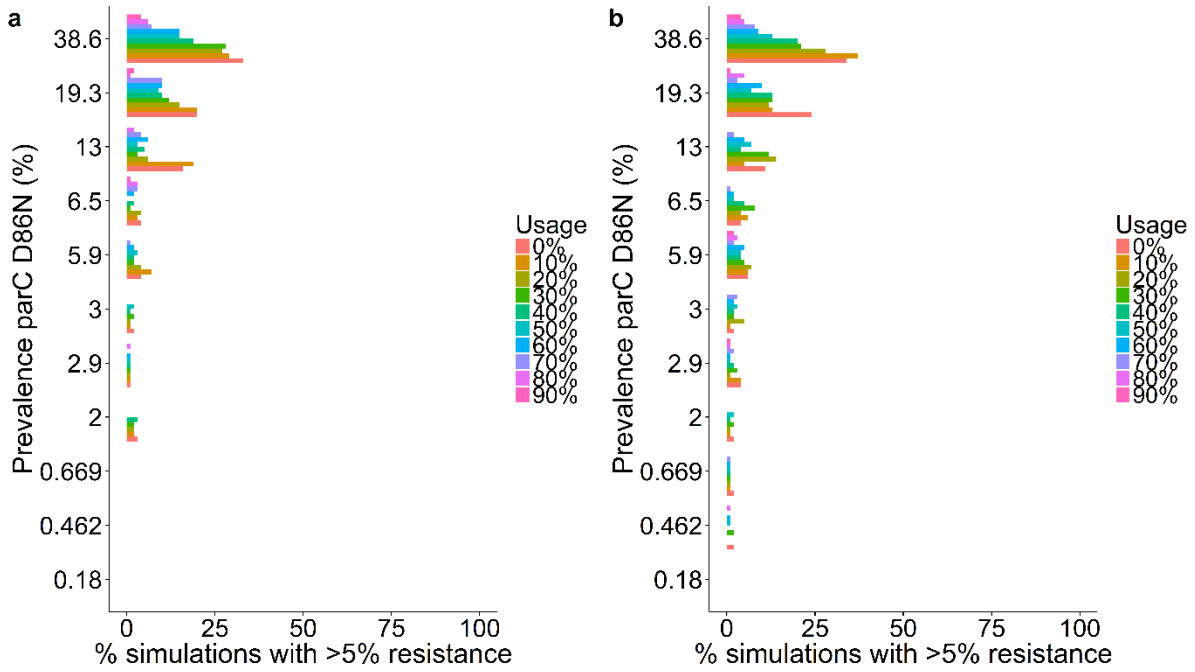
		ciprofloxacin resistance (29-37)
Initial prevalence of GyrA A92T [%]	0, 1	(29-33, 38)
Initial prevalence of double mutant (ParC D86N/GyrA A92T) [%]	0	Assumption, not reported in any dataset

Supplementary Table 3. Whole genome sequencing data sets and prevalence of ParC D86N.

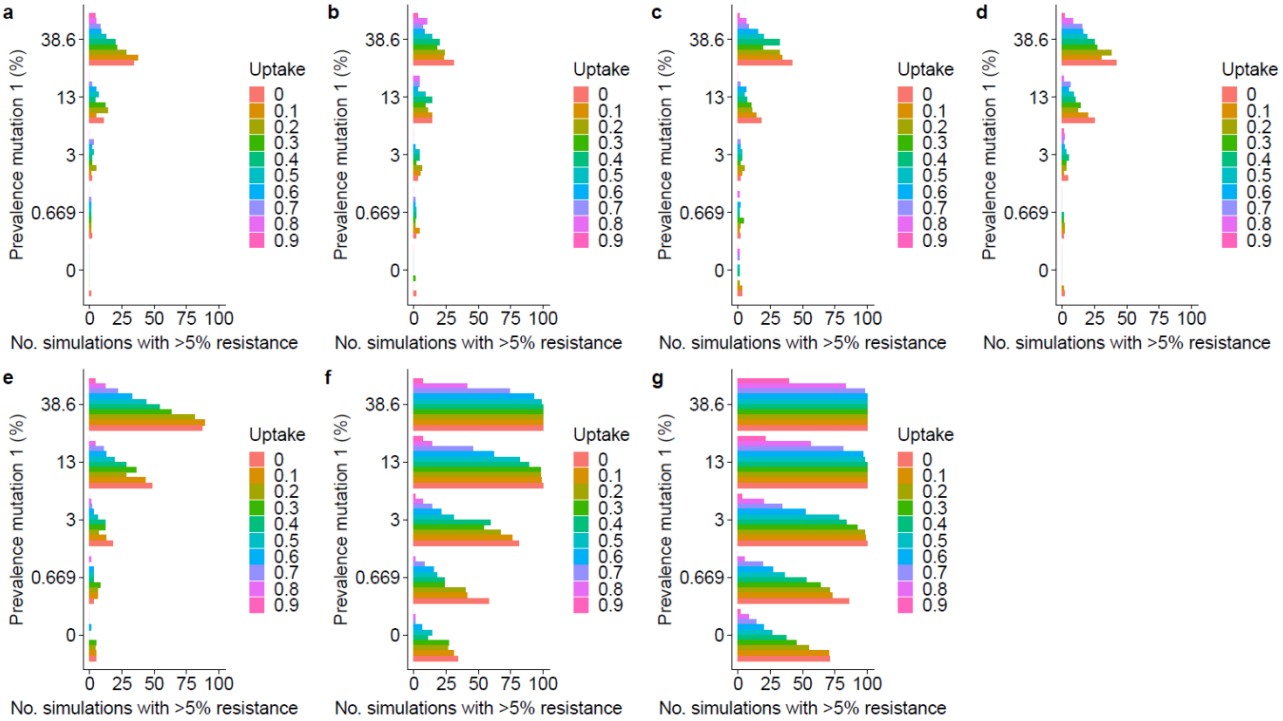
Study	Country	Proportion of Isolates with ParC D86N
Grad et al. 2014 (18), Grad et al. 2016 (39)	United States	0.00636 (7/1100)
Ezewudo et al. 2015 (19)	Global	0.0185 (1/54)
Demczuk et al. 2015 (40)	Canada	0.00840 (1/119)
Demczuk et al. 2016 (41)	Canada	0.0196 (4/204)
De Silva et al. 2016 (42)	United Kingdom	0.0215 (40/1823)
Eyre et al. 2017 (43)	United Kingdom	0.0476 (22/462)
Kwong et al. 2017 (44)	Australia	0.0851 (8/94)
Buckley et al. 2018 (45)	Australia	0 (0/372)
Cehovin et al. 2018 (46)	Kenya	0 (0/103)
Fifer et al. 2018 (47)	United Kingdom	0 (0/50)
Harris et al. 2018 (48)	Europe	0.0442 (46/1041)
Lee et al. 2018 (49)	New Zealand	0.0242 (10/297)
Ryan et al. 2018 (50)	Ireland	0.179 (7/39)
Sánchez-Busó et al. 2018 (51, 52)	Global	0.0548 (21/383)
Yahara et al. 2018 (53)	Japan	0.0923 (24/260)
Peng et al. 2019 (54)	China	0.144 (60/416)
Thomas et al. 2019 (55)	United States	0.0946 (58/613)
Williamson et al. 2019 (56)	Australia	0.114 (249/2181)
Lan et al. 2020 (57)	Vietnam	0.0617 (14/227)
Town et al. 2018 (58)	United Kingdom	0.0691 (88/1274)

Supplementary Table 4: Examples of mutation rate increases with treatment

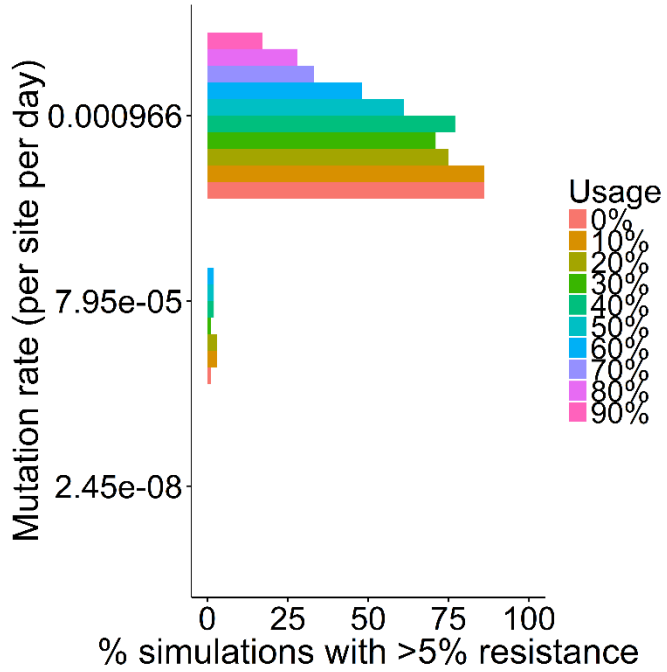
Bacterial species	Antibiotic	Mutation rate or relative increase	Reference
Mycobacterium fortuitum	Ciprofloxacin 0.5MIC	72-120-fold increase	(21)
Streptococcus pneumoniae	Ciprofloxacin 2MIC	1st step 1.1×10^{-9} per nucleotide per replication 2nd step 1.3×10^{-8} per nucleotide per replication	(22)
	Gemifloxacin	1st step 1.6×10^{-11} per nucleotide per replication 2nd step 7.2×10^{-9} per nucleotide per replication	(22)
Pseudomonas aeruginosa	Levofloxacin	0 to >1 in 74000 colonies depending on strain and concentration	(20)
	Ciprofloxacin	0 to >1 in 80000 colonies depending on strain and concentration	(20)
	Quinolone	Frequency of resistant colonies 1.2×10^{-6} to 4×10^{-10} depending on quinolone and concentration	(59)
	Ceftazidime	200-fold increase in mutant cells	(28)
	Ciprofloxacin	50000-fold increase in mutant cells	(28)
	Tobramycin	10-fold increase in mutant cells	(28)
Campylobacter jejuni	Ciprofloxacin 10MIC	≥1.5-fold increase	(23)
Escherichia coli	Norfloxacin	Concentration- and strain-dependent, in the order of 1×10^{-10} to 1×10^{-8} per nucleotide per cell division	(24)
	Ciprofloxacin	Wild-type 7-fold increase Hypoactive mutator strain 1.3-fold increase Hyperactive mutator strain 13-fold increase	(60)
S. aureus	Ciprofloxacin	4.3-fold increase	(27)
	Vancomycin	1.7-2.5-fold increase	(27)



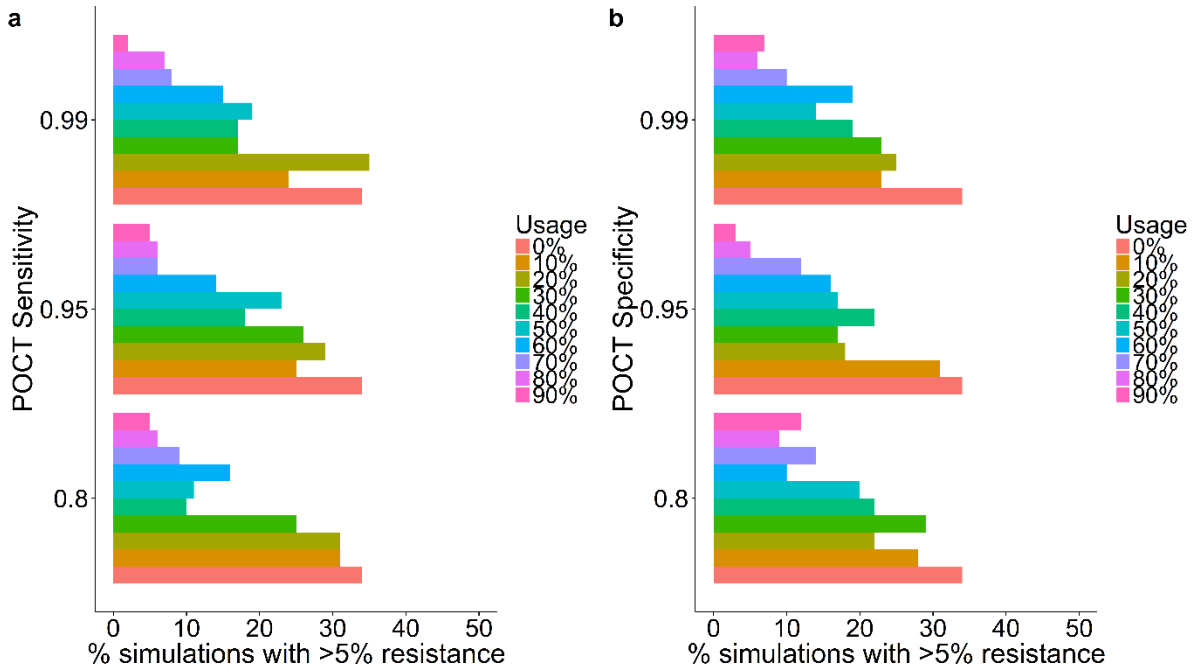
Supplementary Figure 1: Proportion of simulations in which the frequency of gepotidacin-resistant strains reaches 5% with different stepping-stone mutation prevalences and POCT usage levels. The mutation rate with treatment is assumed to be the same as without treatment, 2.45×10^{-8} substitutions per nucleotide per day. a) Prevalence of GyrA A92T is 0. b) Prevalence of GyrA A92T is 1%. There was one simulation in which resistance occurred if mutation 1 had a frequency of 0 and POCT usage was 0%. X-axis: Percentage of simulations in which 5% gepotidacin resistance is reached. Y-axis: prevalence of ParC D86N.



Supplementary Figure 2: Proportion of simulations out of 100 iterations in which the frequency of gepotidacin-resistant strains reaches 5% with different mutation rates, prevalence of ParC D86N and POCT Usage levels. The initial prevalence of GyrA A92T was 1% in all simulations. Mutation rates [substitutions per nucleotide per day]: a) 2.45×10^{-8}, b) 4.9×10^{-8}, c) 1.23×10^{-7}, d) 2.45×10^{-7}, e) 2.45×10^{-6}, f) 2.45×10^{-5}, g) 7.95×10^{-5}. X-axis: number of simulations out of 100 in which 5% gepotidacin resistance is reached. Y-axis: initial prevalence of ParC D86N.



Supplementary Figure 3: Proportion of simulations in which the frequency of gepotidacin-resistant strains reaches 5% with different mutation rates under treatment and POCT Usage levels. Mutation rate without treatment: 2.45×10^{-8} substitutions per nucleotide per day, no pre-existing stepping-stone mutations. X-axis: percentage of simulations in which 5% gepotidacin resistance is reached. Y-axis: mutation rate with treatment [substitutions per nucleotide per day].



Supplementary Figure 4: Proportion of simulations in which the frequency of gepotidacin-resistant strains reaches 5% for different Usage levels of a POCT. Mutation rate with and without treatment 2.45×10^{-8} substitutions per nucleotide per day. Prevalence of ParC D86N: 38.6%, prevalence of GyrA A92T: 1%. a) Y-axis gives assumed POCT sensitivity, b) Y-axis gives assumed POCT specificity. X-axis: percentage of simulations in which 5% gepotidacin resistance is reached.

Supplementary Text 2 – Deterministic model equations, diagrams and possible state transitions

See Table 2 in main text for explanation of model variables and parameters.

Equations 1: General model of gonorrhoea transmission.

$$\frac{dS}{dt} = -\beta S(I_{00} + I_{10} + I_{01} + I_{11}) + f(I_{00} + I_{10} + I_{01} + I_{11}) + g(T_{00} + T_{10} + T_{01})$$

$$\frac{dI_{00}}{dt} = \beta S I_{00} - f I_{00} - \gamma I_{00} + \sigma_b(I_{10} + I_{01} - 2I_{00})$$

$$\frac{dI_{10}}{dt} = \beta S I_{10} - f I_{10} - \gamma I_{10} + \sigma_b(I_{00} + I_{11} - 2I_{10})$$

$$\frac{dI_{01}}{dt} = \beta S I_{01} - f I_{01} - \gamma I_{01} + \sigma_b(I_{00} + I_{11} - 2I_{01})$$

$$\frac{dI_{11}}{dt} = \beta S I_{11} - f I_{11} - \gamma I_{11} + g T_{11} + \sigma_b(I_{10} + I_{01} - 2I_{11})$$

$$\frac{dT_{00}}{dt} = \gamma I_{00} - g T_{00} - 2\sigma_t T_{00}$$

$$\frac{dT_{10}}{dt} = \gamma I_{10} - g T_{10} + \sigma_t(T_{00} - T_{10})$$

$$\frac{dT_{01}}{dt} = \gamma I_{01} - g T_{01} + \sigma_t(T_{00} - T_{01})$$

$$\frac{dT_{11}}{dt} = \gamma I_{11} - g T_{11} + \sigma_t(T_{10} + T_{01})$$

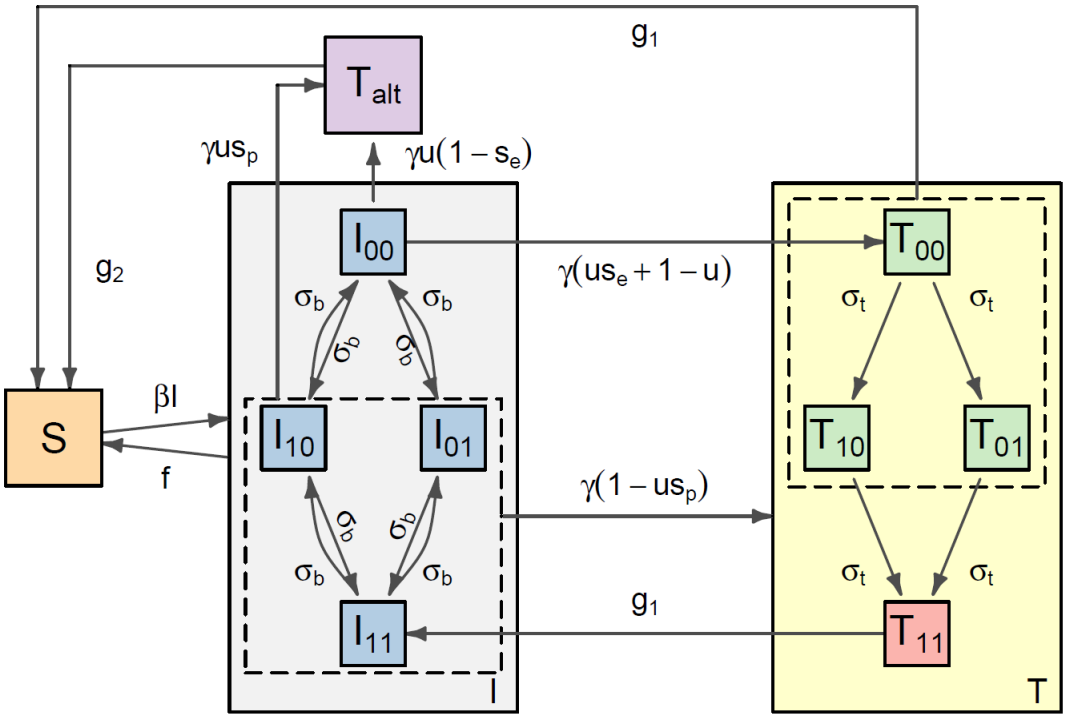


Figure S1: Two-locus gonorrhoea antibiotic resistance model. Point-of-care test (POCT). Gepotidacin is only used for treatment if no resistance mutations are found – otherwise unspecified alternative treatment is used. S – susceptible, I – infected individuals before treatment has been sought, T – infected individuals treated with gepotidacin, T_{alt} – infected individuals treated with alternative antibiotic, subscript 0 – sensitive allele, subscript 1 – resistant allele, β – infection rate parameter, f – recovery rate, γ – treatment rate, g1 – cure rate of gepotidacin, g2 – cure rate of alternative treatment, u – Usage level of POCT, s_e – sensitivity of POCT, s_p – specificity of POCT, σ_b – baseline mutation rate σ_t mutation rate under treatment .

Equations 2: Point-of-care test. See Caption of Figure S1 for explanation of model variables and parameters.

$$\frac{dS}{dt} = -\beta S(I_{00} + I_{10} + I_{01} + I_{11}) + f(I_{00} + I_{10} + I_{01} + I_{11}) + g_1(T_{00} + T_{10} + T_{01}) + g_2 T_{alt}$$

$$\frac{dI_{00}}{dt} = \beta S I_{00} - f I_{00} - \gamma I_{00} + \sigma_b(I_{10} + I_{01} - 2I_{00})$$

$$\frac{dI_{10}}{dt} = \beta S I_{10} - f I_{10} - \gamma I_{10} + \sigma_b(I_{00} + I_{11} - 2I_{10})$$

$$\frac{dI_{01}}{dt} = \beta S I_{01} - f I_{01} - \gamma I_{01} + \sigma_b(I_{00} + I_{11} - 2I_{01})$$

$$\frac{dI_{11}}{dt} = \beta S I_{11} - f I_{11} - \gamma I_{11} + g_1 T_{11} + \sigma_b(I_{10} + I_{01} - 2I_{11})$$

$$\frac{dT_{00}}{dt} = [us_e\gamma + (1-u)\gamma]I_{00} - g_1T_{00} - 2\sigma_tT_{00}$$

$$\frac{dT_{10}}{dt} = [u(1-s_p)\gamma + (1-u)\gamma]I_{10} - g_1T_{10} + \sigma_t(T_{00} - T_{10})$$

$$\frac{dT_{01}}{dt} = [u(1-s_p)\gamma + (1-u)\gamma]I_{01} - g_1T_{01} + \sigma_t(T_{00} - T_{01})$$

$$\frac{dT_{11}}{dt} = [u(1-s_p)\gamma + (1-u)\gamma]I_{11} - g_1T_{11} + \sigma_t(T_{10} + T_{01})$$

$$\frac{dT_{alt}}{dt} = us_p\gamma(I_{10} + I_{01} + I_{11}) + u(1-s_e)\gamma I_{00} - g_2T_{alt}$$

Table S1: Point-of-care test. Possible state transitions in individual-based stochastic model based on the deterministic equations detailed above. See Caption of Figure S1 for explanation of model variables and parameters.

Current state	**Possible transitions**
S	$S \rightarrow I_{00}$, $S \rightarrow I_{10}$, $S \rightarrow I_{01}$, $S \rightarrow I_{11}$
I_{00}	$I_{00} \rightarrow S$, $I_{00} \rightarrow T_{00}$, $I_{00} \rightarrow T_{alt}$, $I_{00} \rightarrow I_{10}$, $I_{00} \rightarrow I_{01}$
I_{10}	$I_{10} \rightarrow S$, $I_{10} \rightarrow T_{10}$, $I_{10} \rightarrow T_{alt}$, $I_{10} \rightarrow I_{00}$, $I_{10} \rightarrow I_{11}$
I_{01}	$I_{01} \rightarrow S$, $I_{01} \rightarrow T_{01}$, $I_{01} \rightarrow T_{alt}$ $I_{01} \rightarrow I_{00}$, $I_{01} \rightarrow I_{11}$
I_{11}	$I_{11} \rightarrow S$, $I_{11} \rightarrow T_{11}$, $I_{11} \rightarrow T_{alt}$, $I_{11} \rightarrow I_{10}$, $I_{11} \rightarrow I_{01}$
T_{00}	$T_{00} \rightarrow S$, $T_{00} \rightarrow T_{10}$, $T_{00} \rightarrow T_{01}$
T_{10}	$T_{10} \rightarrow S$, $T_{10} \rightarrow T_{11}$
T_{01}	$T_{01} \rightarrow S$, $T_{01} \rightarrow T_{11}$
T_{11}	$T_{11} \rightarrow I_{11}$
T_{alt}	$T_{alt} \rightarrow S$

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