UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL ATOMIC ENERGY AGENCY
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

SMR.940 - 35

THIRD AUTUMN WORKSHOP ON MATHEMATICAL ECOLOGY

(14 October - 1 November 1996)

"The dynamics of drug action on within-host pathogen population dynamics"

Daren J. Austin
Department of Zoology
University of Oxford
Oxford OX1 3PS
United Kingdom

These are preliminary lecture notes, intended only for distribution to participants.

Pharmacokinetics?

1. PK is the measurement and modelling of drug concentrations within the body.
2. Required for licensing, efficacy and toxicity studies.
3. Evaluation of possible therapeutic dosage regimens (how much, how often?).
4. Lots of data available from both volunteer and patient studies.

Possible models

1. Single intravenous (IV) dose (first-order decay).
2. Single oral or Intramuscular (IM) dose.
3. Constant dose-rate regimens.
4. Multiple dose regimens.

Pharmacodynamics

1. PD describes the effect of a drug at the active site for a given concentration.
2. Often the exact model of action a drug is unknown (e.g. antimalarials).
3. E_{max} saturation model of drug action is commonly used
4. Data available for antibiotics and antimalarials is all *in vitro*.

Within-host pathogen models

1. Often simple exponential growth models are sufficient.
2. PD couples within-host pathogen models with PK giving treatment models.

Modelling malaria infections

1. Population biology ecological model of malaria infection.
2. Dynamics defined by parameter R_0 which measures the number of secondary infected RBCs in a naïve host produced by a single infected RBC.
3. Drug intervention makes R_0 concentration dependent.
4. Successful prophylaxis/therapy requires $R_0(C) < 1$.
5. Using PD and then PK gives the minimum doses required for success.

References for further reading

1. Rowland, M. & Tozer, T.N. (1995), *Clinical Pharmacokinetics*, Wilkins (in RSL).
2. White, N.J. (1994), Clinical pharmacokinetics and pharmacodynamics of artemisinin and derivatives, *Trans. R. Soc. Trop. Med. Hyg.*, **88**, S1, 41--43.
3. Gravenor, M.B., McLean, A.R. & Kwiatkowski, D. (1995), The regulation of malaria parasitaemia: parameter estimation for a population model, *Parasitology*, **110**, 115-122.
4. Austin, D.J., White, N.J. & Anderson, R.M. (1996), The dynamics of drug action on the within-host pathogen population growth of infectious agents, *J. Theor. Biol.*, **in press**.

provided elsewhere (N.I.S., C.A.B.B., Leeuwen, R.S., and R.J.d.B., unpublished
phase 4% of resting T cells get activated—
the healthy CD4 T-cell count is ~1000 cells,
lls; resting T cells are long-lived (26)—i.e.,
activated T cells rapidly revert to the resting
day; the infection rate is arbitrarily set to γ
led particle per day; the life-time of infected
4, 25)—i.e., $d_I = 0.5$. Setting $\alpha = 0.04$, $d_T =$
ve obtain exactly the same rates of CD4 cell
ecently reported (24, 25).

ance of the mutant strains have previously
ed to be $R_{41} = 4$, $R_{70} = 8$, $R_{215} = 16$, $R_{41/70}$
and $R_{70/215} = 6$ (4, 27). We conservatively
he absence of the drug to $e_{215} = e_{41/215} =$
strains involving the 215 mutation. For the
t $e_{41} = e_{70} = e_{41/70} = 0.95$ to prevent a too
of the first mutations in our model (N.I.S. *et*
ta). The mutation frequencies are estimated
leotide changes they involve. While it is well
G to A changes are preferred over other
s that transitions are more likely to occur
(28). We therefore set the mutation rate of
to 3×10^{-5} (i.e., the basic error rate of RT
G changes to $\mu_1/2$, and other changes to
double nucleotide mutations is the product
ar single nucleotide rates involved. Because
ong, the probability that no mutations occur
$- \mu_1)^{1680} = 0.95$.

RESULTS

cyte Counts. The mean $CD4^+$ cell count
ntly during the first month of treatment, but
baseline values during subsequent months
ial changes in $CD4^+$ cell count mirrored the
HIV-1 RNA load.

NA load. Serum HIV-1 RNA was detectable
ll time points with a mean level at baseline
nl (±0.43) (Fig. 1*B*). A maximum decline of
nth was followed by increases during subse-
though still significantly below baseline val-
s, mean RNA load reached baseline values
of treatment.

nts of 41, 70, and 215 Mutant Serum HIV-1
ntage of 70 mutant RNA could not be
ubject, possibly due to sequence variation of
nnealing site of the probe. In the remaining
odon 70 change generally was the first to
After 2 years, the median percentage of 70
decreased to <5% with a concurrent
centage of [illegible] RNA. This result
ved within this study. Although appearing
[illegible]
hout the

epresents the general pattern, marked dif-
ndividuals were observed in the rate of
215 codon change (with or without the 41
ects developing the codon 215 change
eemed to have a slightly lower baseline

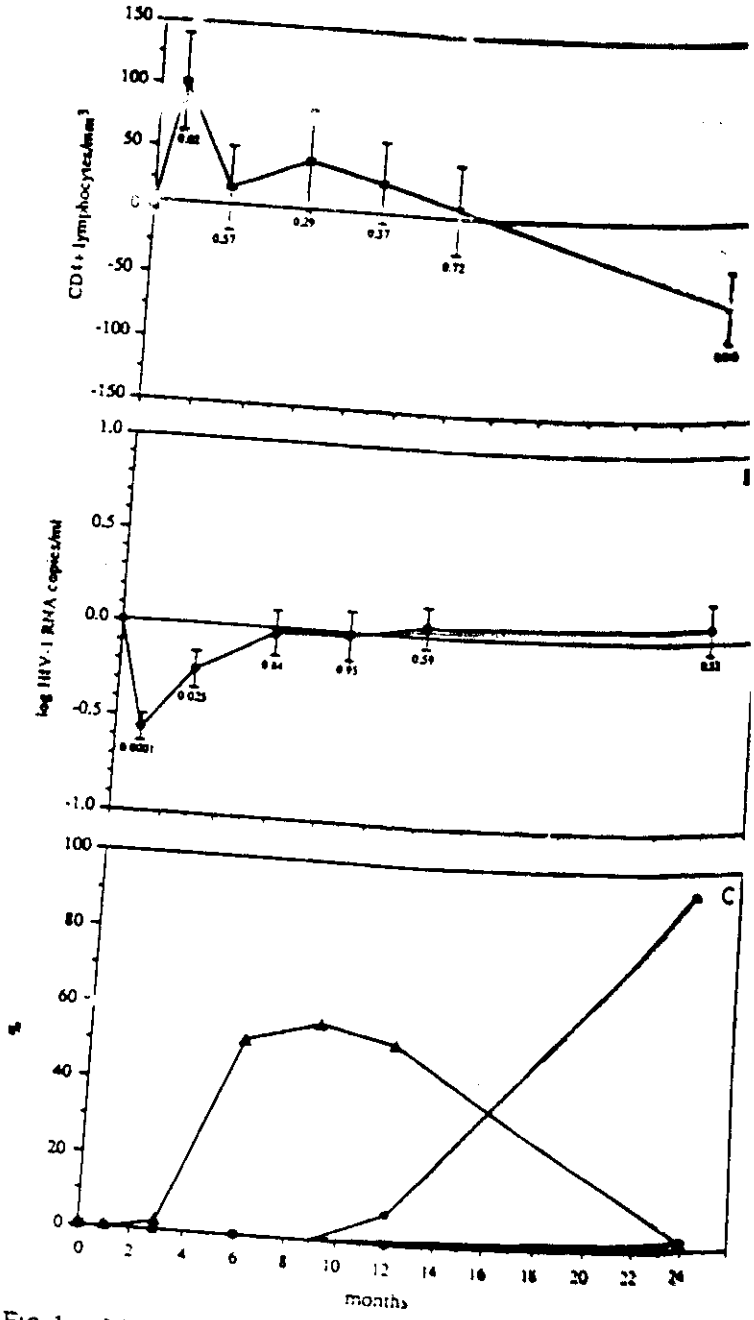


FIG. 1. Mean changes from baseline (±SE) in (*A*) $CD4^+$ cell count (*B*), log HIV-1 RNA load, and (*C*) median percentages of HIV-1 RNA containing a M41L (■), K70R (▲), and T215Y/F (●) amino acid change in HIV-1 RT during 2 years of zidovudine treatment. Numbers underneath error bars indicate the *P* values of changes (paired two-tailed *t* test).

HIV-1 RNA Load Changes and Resistance Mutations. A temporal relationship appeared to exist between the emergence of K70R mutant virus and a return to baseline values of serum RNA load (Fig. 1). Because it was not clear whether the relative amounts of 70 mutant RNA were sufficient to explain

[illegible] of 70
[illegible] first 9 months of [illegible] other muta-
[illegible] generally not appear (Fig. 2).

The initial increase of serum RNA load between 1 and 3 months of treatment was not caused by the K70R amino acid change, because a similar resurgence was observed in 70 wild-type virus. However, the ultimate increase to baseline

PHARMACOKINETICS & PHARMACODYNAMICS.

DAREN AUSTIN.

(I) PHARMACOKINETICS

- MEASUREMENT AND MODELLING OF DRUG CONCENTRATIONS WITHIN THE BODY.
- REQUIRED FOR LICENSING, EFFICACY AND TOXICITY STUDIES.
- EVALUATION OF POSSIBLE DOSAGE REGIMES.
- LOTS OF DATA.

MODELS

- SINGLE I.V. DOSE (FIRST-ORDER ELIMINATION).

• VOLUME OF DISTRIBUTION $V = \dfrac{\text{AMOUNT OF DRUG IN BODY}}{\text{PLASMA DRUG CONCENTRATION}}$

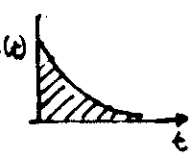
$$V = \frac{A}{C}$$

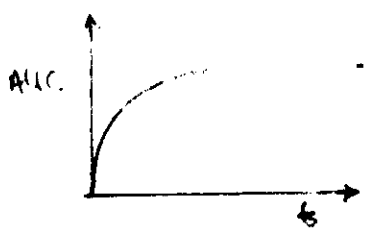
$$\frac{dC}{dt} = -kC \Rightarrow C(t) = C(0)\exp(-kt). \quad \times V$$

$$A(t) = \text{DOSE}\exp(-kt).$$

• $t_{1/2} = \dfrac{\ln_e 2}{k}$ → ESTIMATION OF k FROM $t_{1/2}$.

• AREA UNDER CURVE $AUC = \int_0^t dt'\, C(t).$

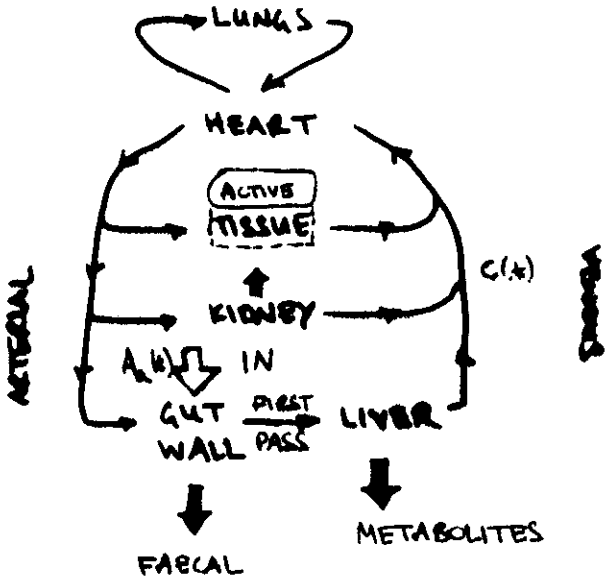




• CLEARANCE = RATE OF DRUG ELIMINATION $CL = \dfrac{\text{DOSE}}{AUC}$

– SINGLE ORAL / I.M. DOSE (FIRST-ORDER ABSORPTION)

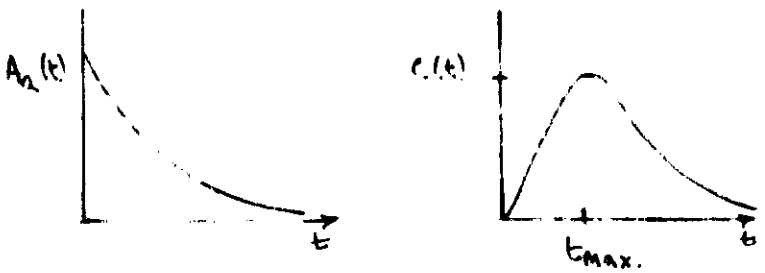
• BIOAVAILABILITY F = FRACTION OF DOSE ABSORBED INTACT;



$$\frac{dA_a}{dt} = -k_a A_a \qquad \frac{dC}{dt} = \frac{k_a A_a}{V} - kC$$

$$A_a(t) = F\,\text{DOSE}\,\exp(-k_a t)$$

$$C(t) = \frac{F\,\text{DOSE}}{V}\,\frac{k_a}{k_a - k}\left[\exp(-kt) - \exp(-k_a t)\right]$$



– MULTIPLE COMPARTMENT MODELS.

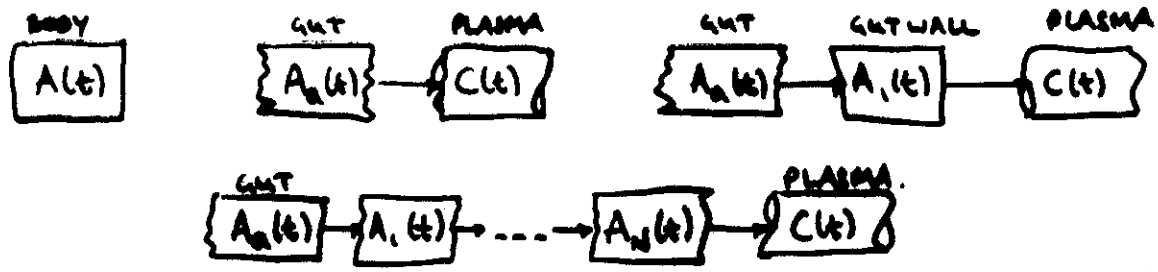
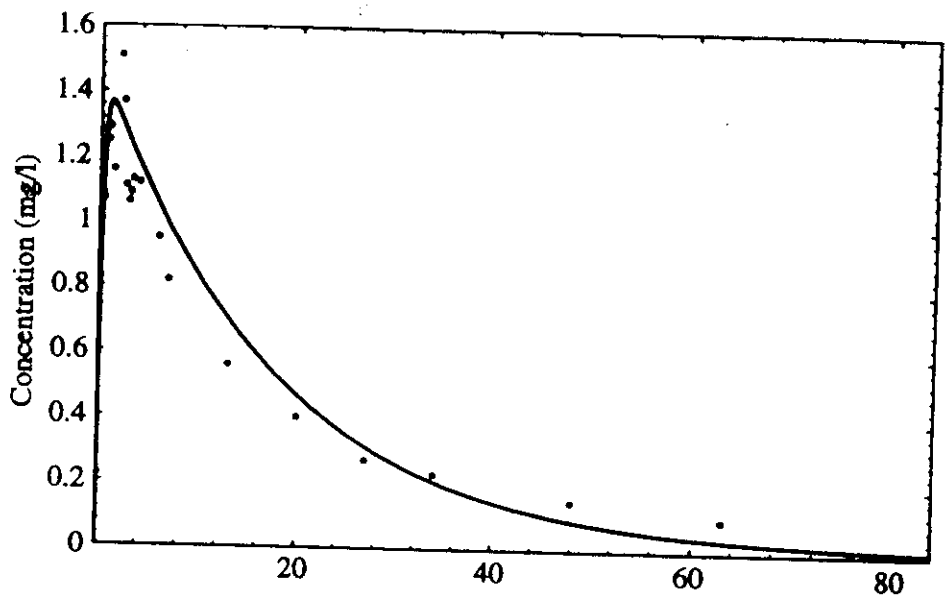


Figure 1.

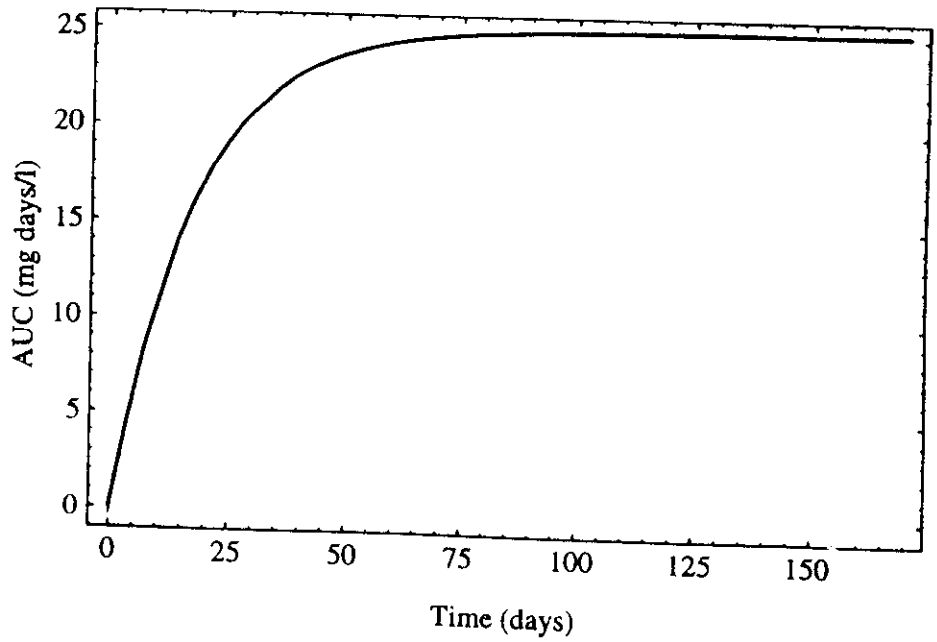
a/

Plasma mefloquine concentration (1500mg dose)



b/

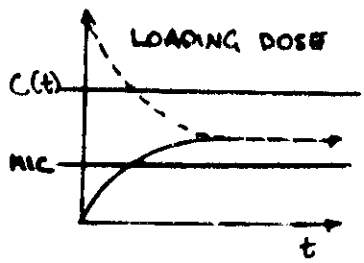
Mefloquine Area Under Curve (1500mg dose)



① — CONSTANT DOSE-RATE REGIMENS.
② — MULTIPLE DOSE REGIMENS.
} → THERAPEUTIC PLASMA

① DOSE RATE = $\mathcal{D}_0$ (mg/h).

$$\frac{dC}{dt} = \frac{\mathcal{D}_0}{V} - kC \rightarrow C(t) = \frac{\mathcal{D}_0}{kV}\left(1 - \exp(-kt)\right).$$



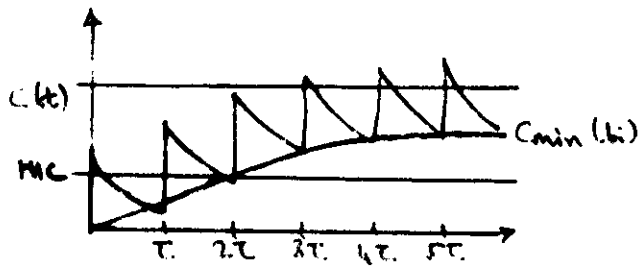
$C(t) \rightarrow \frac{\mathcal{D}_0}{kV}$

② CONSTANT DOSE TAKEN EVERY τ HOURS.

ASSUME I.V. DOSING.

TIME	A(t) / DOSE
0	0
τ	$\exp(-k\tau)$
2τ	$\exp(-k\tau)[1 + \exp(-k\tau)]$
⋮	⋮
$N\tau$	$\exp(-k\tau)[1 + \exp(-k\tau) + \ldots + \exp(-(N-1)k\tau)$.

$$A_{min}(t_i) = \text{DOSE}\ \frac{\left(1 - \exp(-ik\tau)\right)}{\left(1 - \exp(-k\tau)\right)}\ \exp(-k\tau)$$



$$A_{min} \rightarrow \text{DOSE} \cdot \frac{\exp(-k\tau)}{1 - \exp(-k\tau)} = \frac{\mathcal{D}_0}{k}$$

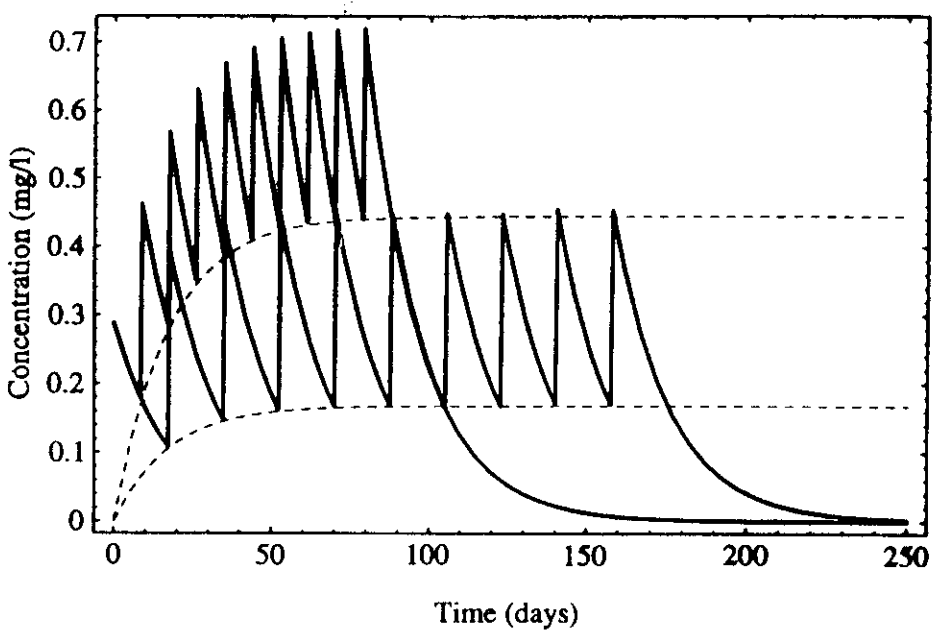
⇒ EQUIVALENT WHEN $\mathcal{D}_0 =$ k DOSE $\exp(-k\tau)$. $\mathcal{R}$.

- $\mathcal{R}$ = ACCUMULATION FACTOR FOR THE REGIMEN.

Figure 3.

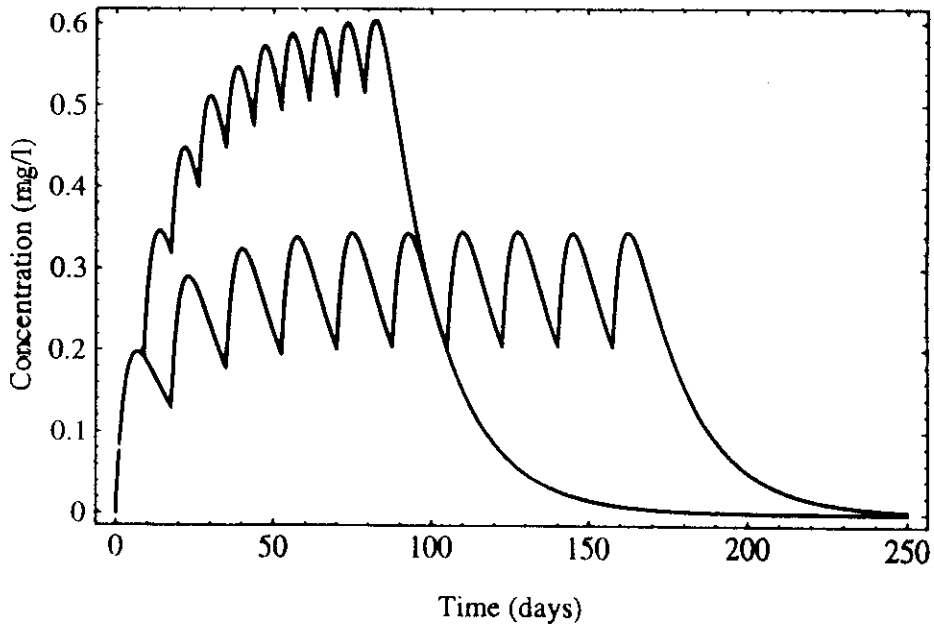
a/

Plasma mefloquine concentration (250mg oral dose)



b/

Plasma mefloquine concentration (250mg slow absorption)



(II) PHARMACODYNAMICS.

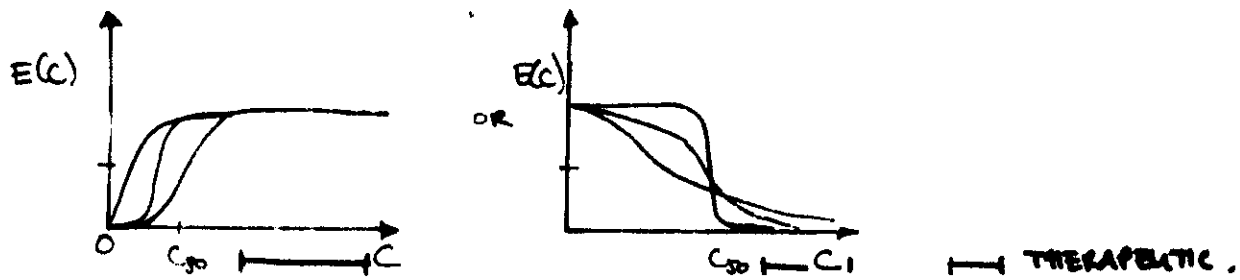
— DESCRIBES THE CONCENTRATION – EFFECT RELATIONSHIP AT THE ACTIVE SITE.

— EXACT MODE OF ACTION IS OFTEN UNKNOWN.

— E_{MAX} MODEL.

- $\text{EFFECT}(c) = \dfrac{E_{MAX}\, C^n}{C_{50}^n + C^n}$ INCREASED EFFECT.

$= \text{NODRUG} - \dfrac{E_{MAX}\, C^n}{C_{50}^n + C^n}$ DECREASED.



— ANTIMALARIAL DRUGS KILL INFECTED RBC. (INCREASE)

— ANTIBIOTICS INHIBIT REPLICATION (REDUCE).

— DATA IS FROM *IN VITRO* STUDIES ONLY.

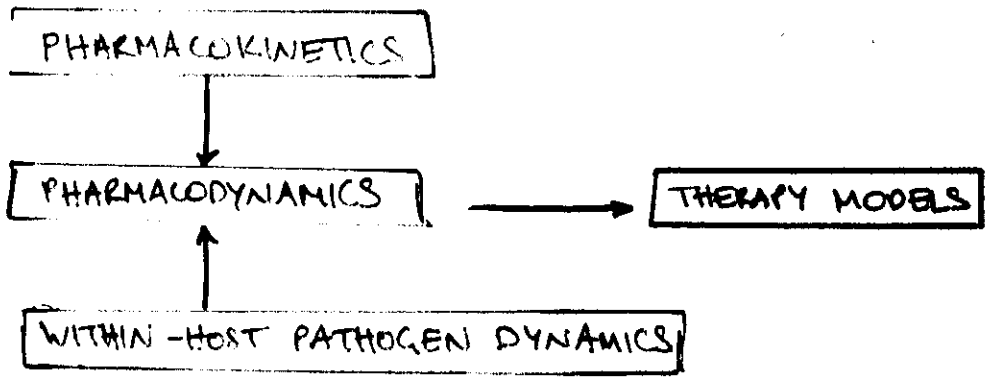
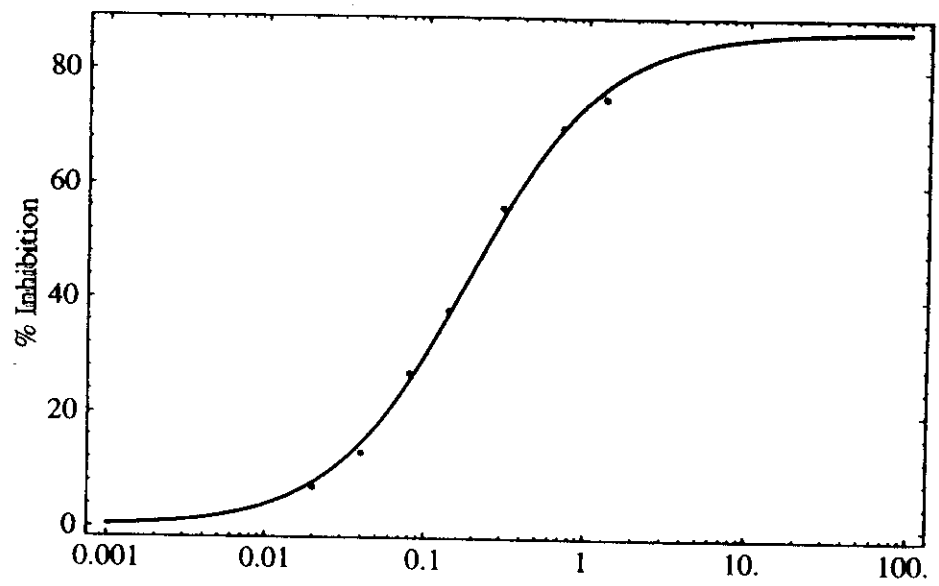
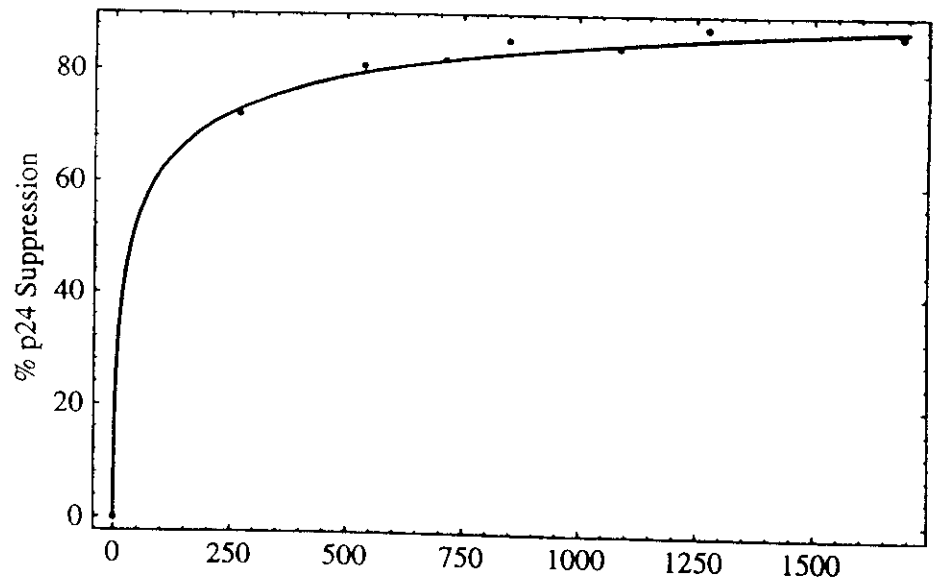


Figure 2

Mefloquine inhibition of T996 P. falciparum



ddI suppression of p24 HIV antigen



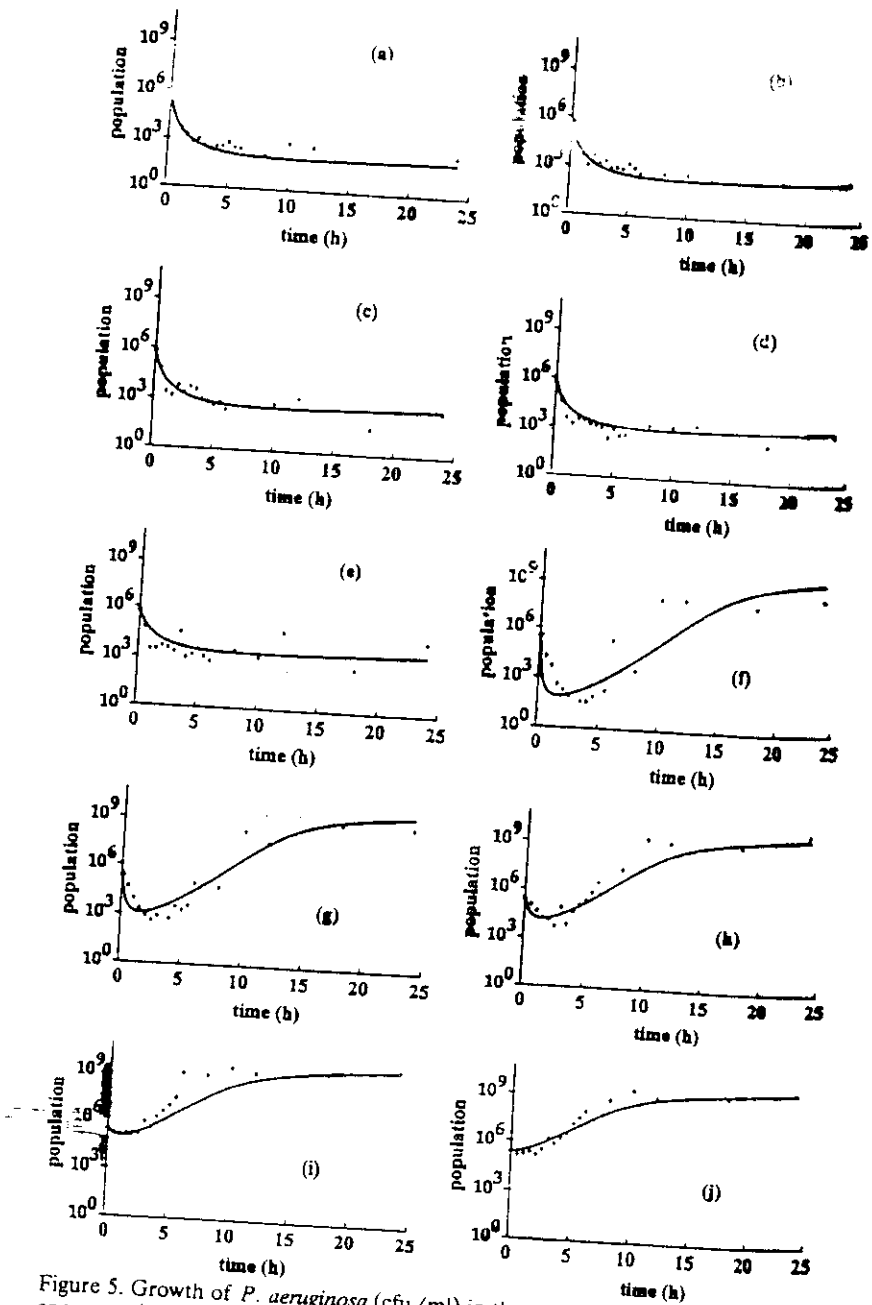
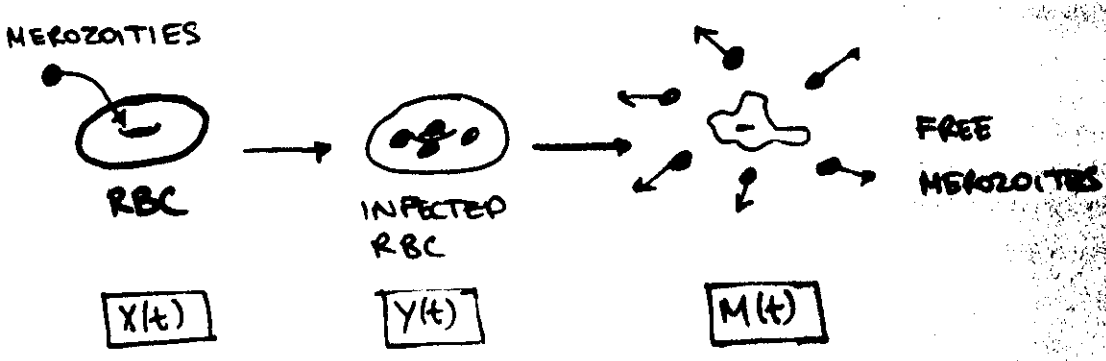


Figure 5. Growth of *P. aeruginosa* (cfu/ml) in the presence of imipenem. Initial concentrations of (a) 64, (b) 32, (c) 16, (d) 8, (e) 4, (f) 2, (g) 1, (h) 0.5, (i) 0.25 and (j) 0.125 μg/ml. Parameter values for U5 are used for graphs (a)–(e); parameter values for L5 are used for graphs (f)–(j). The points show the experimental data; the solid line shows the fitted curve.

(IV) MALARIA.

- NO IMMUNITY MODEL;



$$\frac{dX}{dt} = A - \mu X - \underbrace{\beta X M}_{\text{INFECTION}}$$

$$\frac{dY}{dt} = \beta X M - \underbrace{\alpha Y}_{\text{INCREASED DEATH RATE WHEN INFECTED}}$$

$$\frac{dM}{dt} = \underbrace{r\alpha Y}_{\substack{\text{CELL} \\ \text{RUPTURES}}} - \delta M - \beta' X M.$$

$\alpha(c)$ WITH DRUGS.

$r(c)$ WITH DRUGS.

- MALARIA INVADES IF

$$\boxed{R_0 = \frac{A}{\mu}\frac{\beta(r-1)}{\delta} > 1}.$$

$\frac{A}{\mu}$ = HAEMATOCRIT.

- PROPHYLAXIS REQUIRES $R_0 < 1$.

- CHEMOPROPHYLAXIS MAKES $R_0(c)$, CONCENTRATION DEPENDENT.

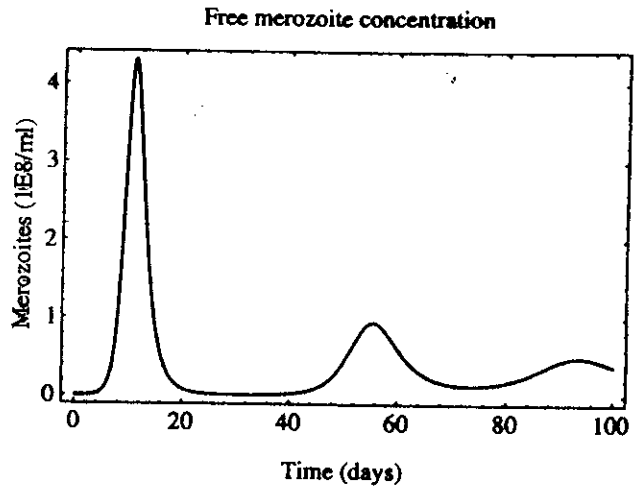
  - CALCULATE PLASMA DRUG CONCENTRATION REQUIRED SUCH THAT $R_0(c) < 1$

- IMMUNITY REDUCES R_0.

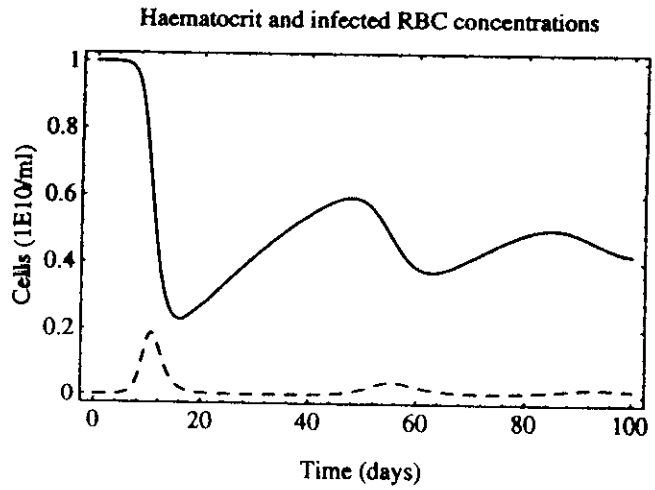
$$R_0 = \frac{A}{\mu}\frac{\beta(r-1-I)}{\delta(1+I)} \geq 1$$

Fig 9.

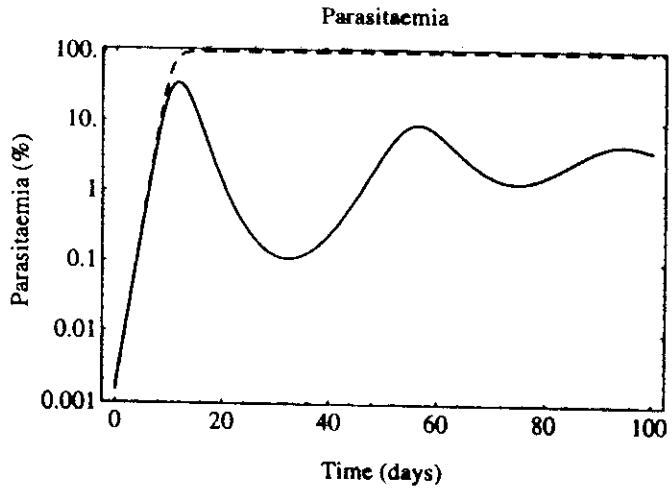
a/

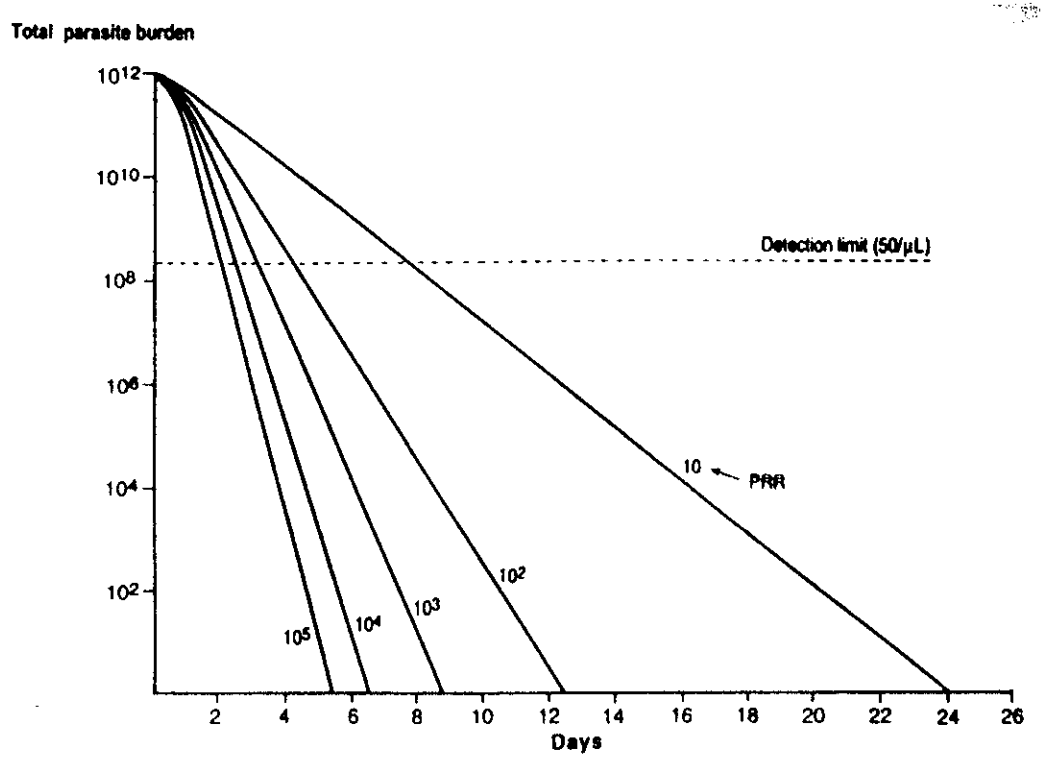

Free merozoite concentration
Merozoites (1E8/ml)
0
1
2
3
4
0
20
40
60
80
100
Time (days)

b/


Haematocrit and infected RBC concentrations
Cells (1E10/ml)
0
0.2
0.4
0.6
0.8
1
0
20
40
60
80
100
Time (days)

c/


Parasitaemia
Parasitaemia (%)
100.
10.
1
0.1
0.01
0.001
0
20
40
60
80
100
Time (days)


Total parasite burden
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
Detection limit (50/μL)
10
PRR
10^{2}
10^{3}
10^{4}
10^{5}
2 4 6 8 10 12 14 16 18 20 22 24 26
Days

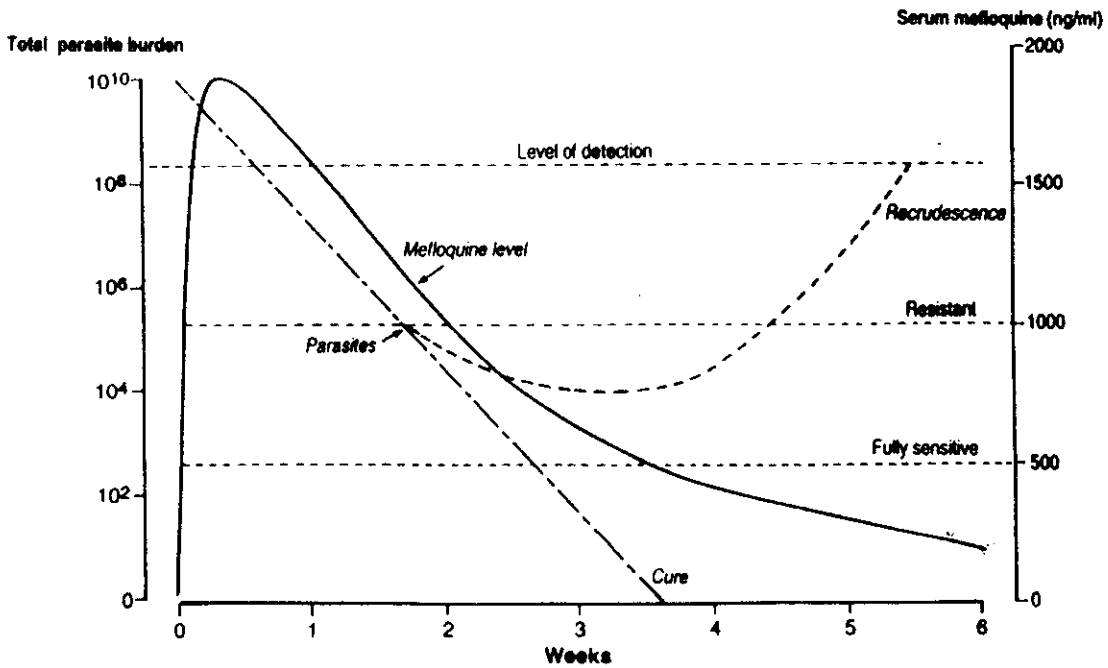
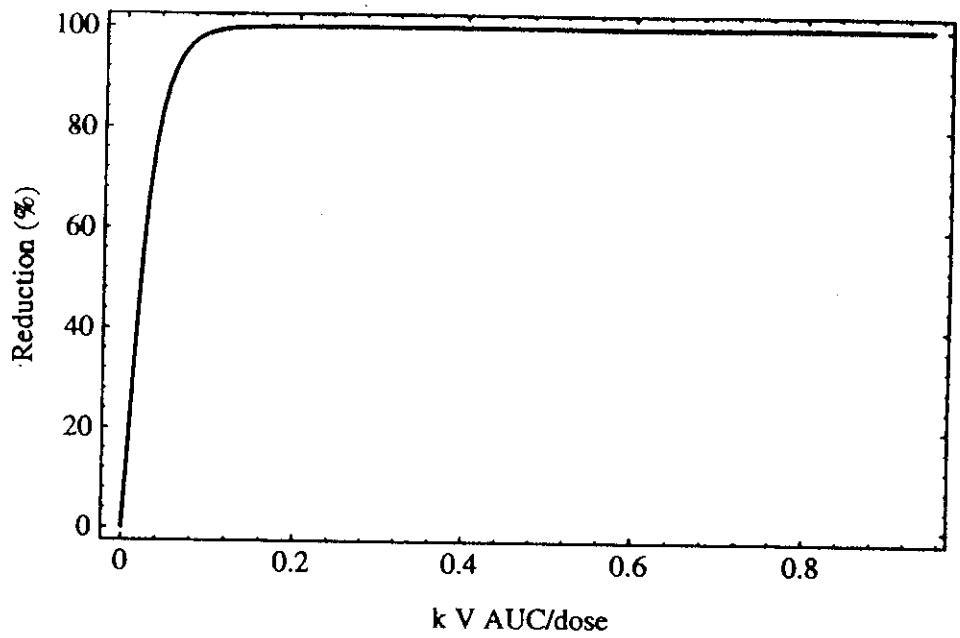

Total parasite burden
Serum mefloquine (ng/ml)
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
0
2000
1500
1000
500
0
Level of detection
Recrudescence
Mefloquine level
Resistant
Parasites
Fully sensitive
Cure
0 1 2 3 4 5 6
Weeks

Figure 11

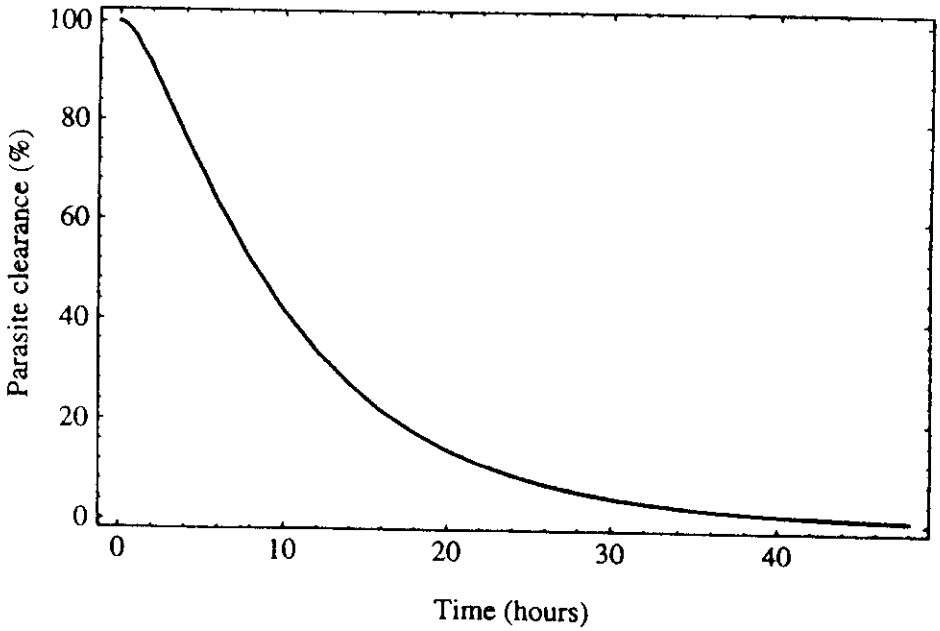
a/

Percentage parasite reduction



b/

Population parasite clearance curve



Self-limiting

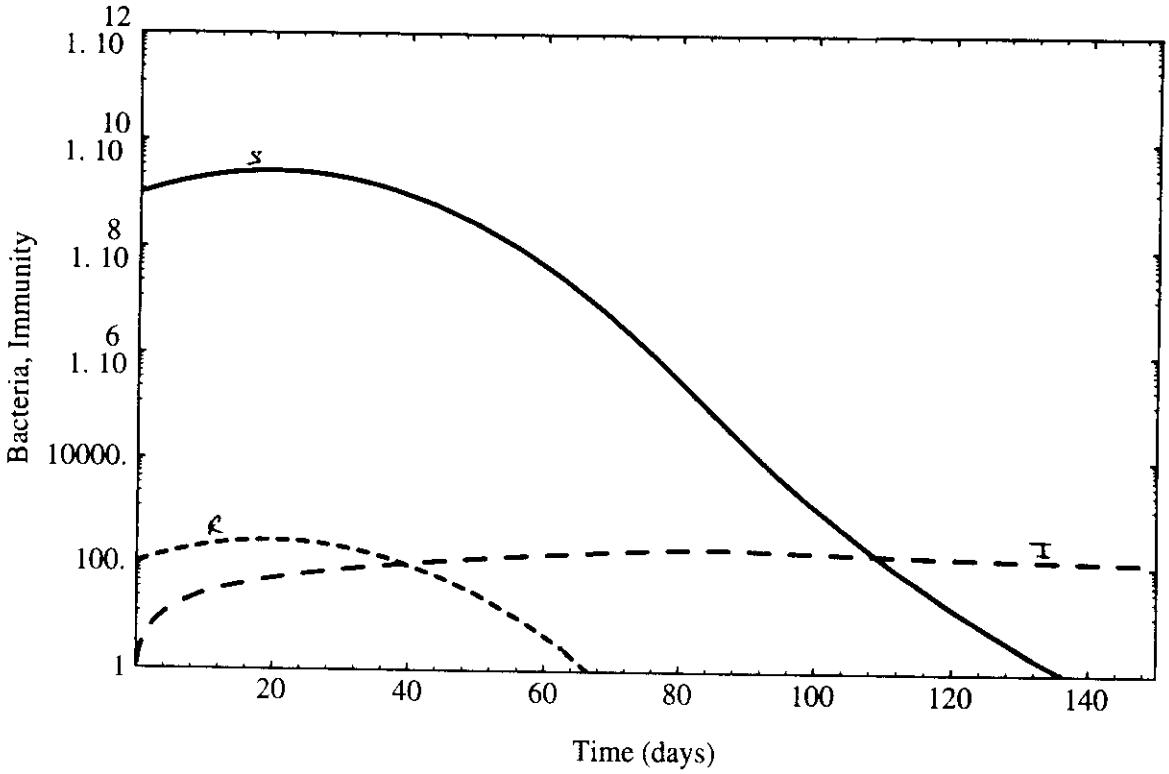
Simple Model of Bacterial Infection

$$\frac{dS}{dt} = (\lambda_S - \gamma I)S$$ Sensitive

$$\frac{dR}{dt} = (\lambda_R - \gamma I)R$$ Resistant

$$\frac{dI}{dt} = \Lambda - \mu I + \frac{\rho (R+S)}{b_{50} + (R+S)}$$ Immunity

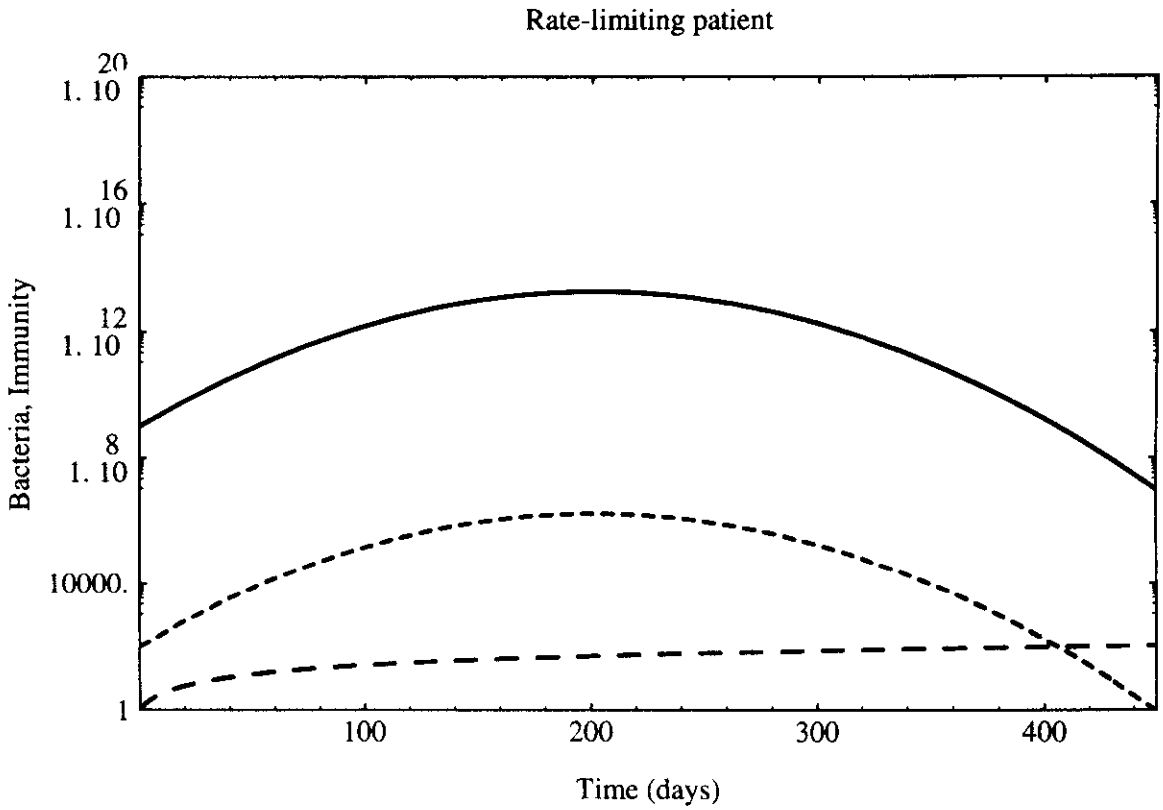
Proliferation



1/ Patient Recovers naturally.

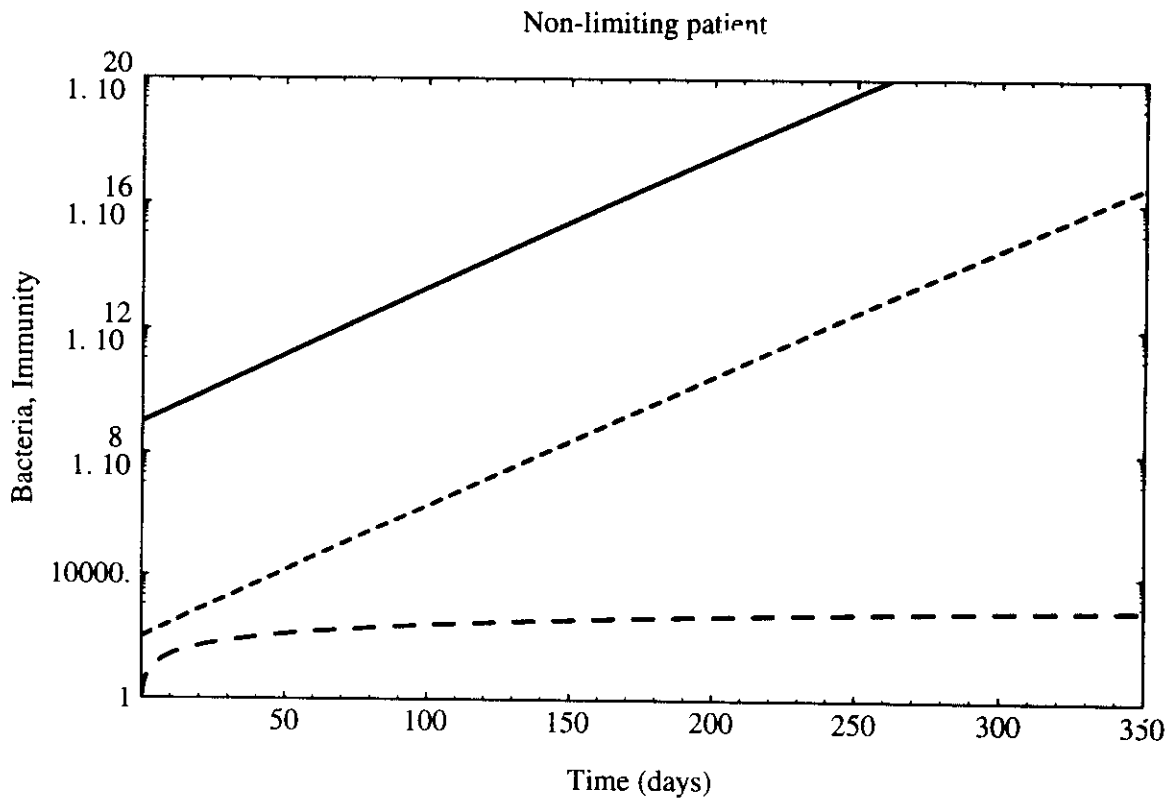
2/ MOST infections are in this class !

3/ Resistant strains are present at low concentrations naturally in the environment (for most antibiotics)



Patient recovers but only after HIGH levels of pathogen

Unan.m

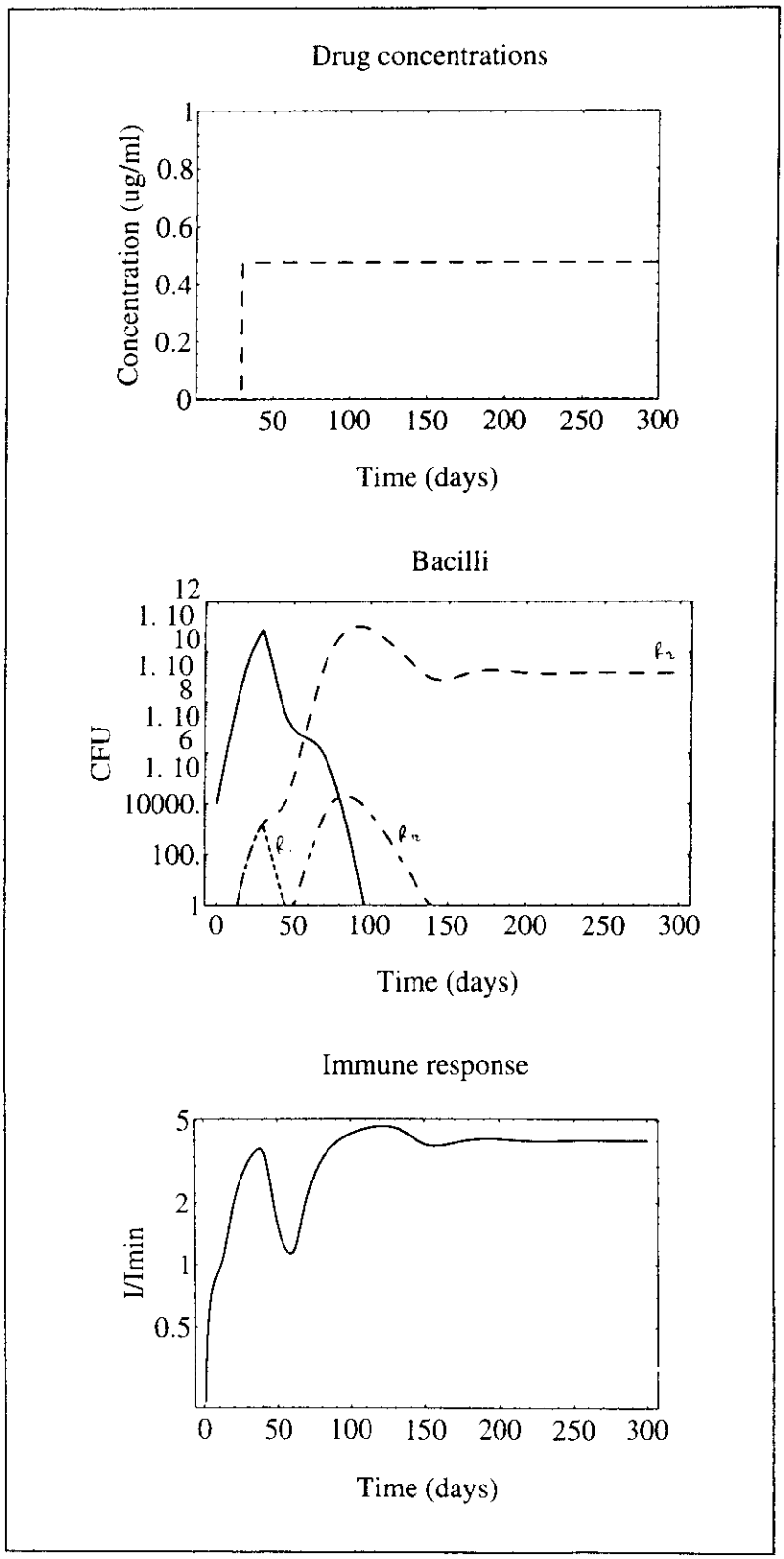


Patient cannot clear infection as Immunity above and requires URGENT treatment.

These 5 models of TB infection in an Immunocompromised patient show how MULTIPLE resistance is difficult to avoid

$\frac{dS}{dt} = (\lambda_S - \gamma I)S$, $\frac{dR_1}{dt} = (\lambda_{R_1} - \gamma I)R_1$, $\frac{dR_2}{dt} = (\lambda_{R_2} - \gamma I)R_2$, $\frac{dR_{12}}{dt} = (\lambda_{R_{12}} - \gamma I)R_{12}$ ← multiply resistant

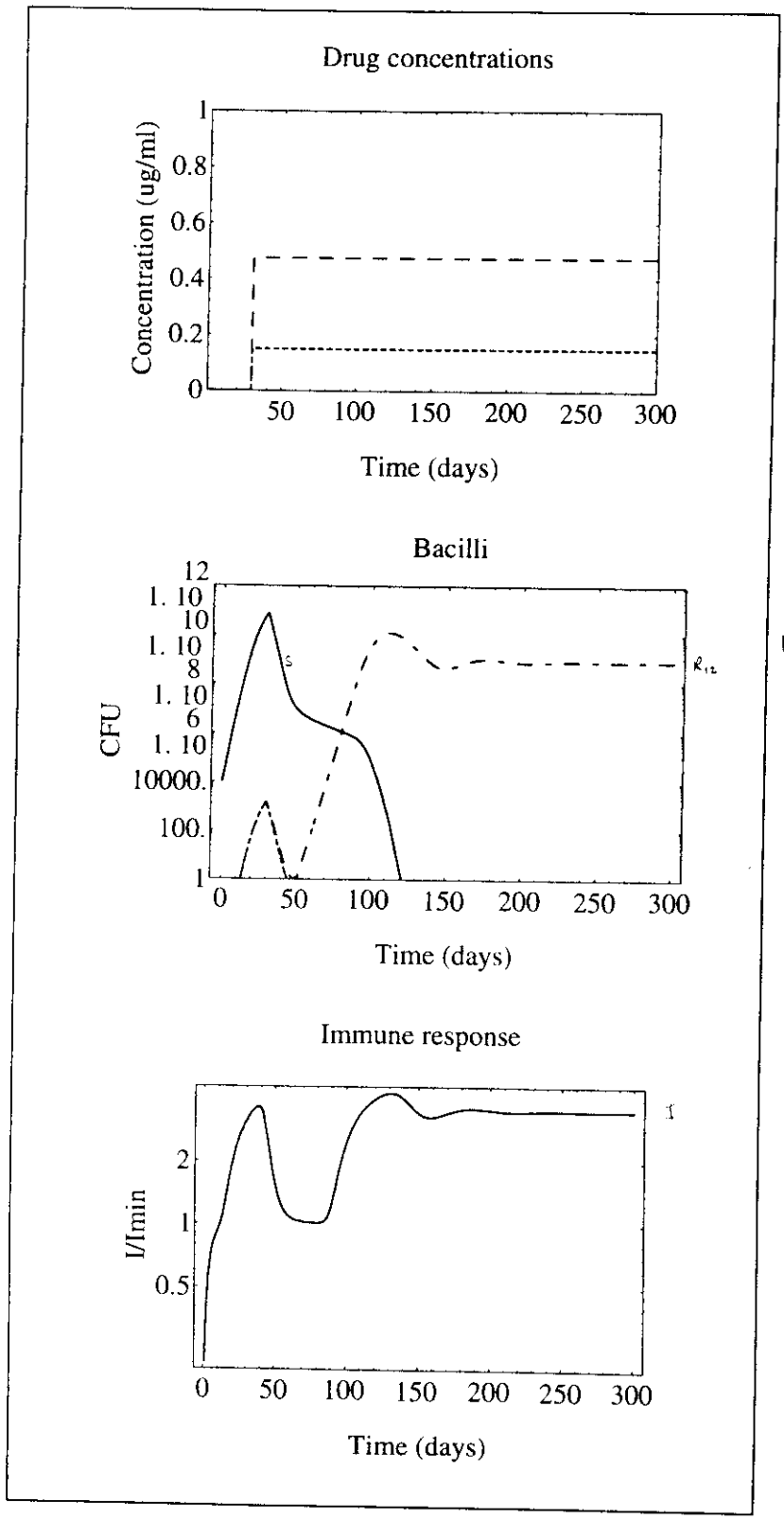
Continuous Rifampin treatment



continuous monotherapy

Resistant to Drug 2

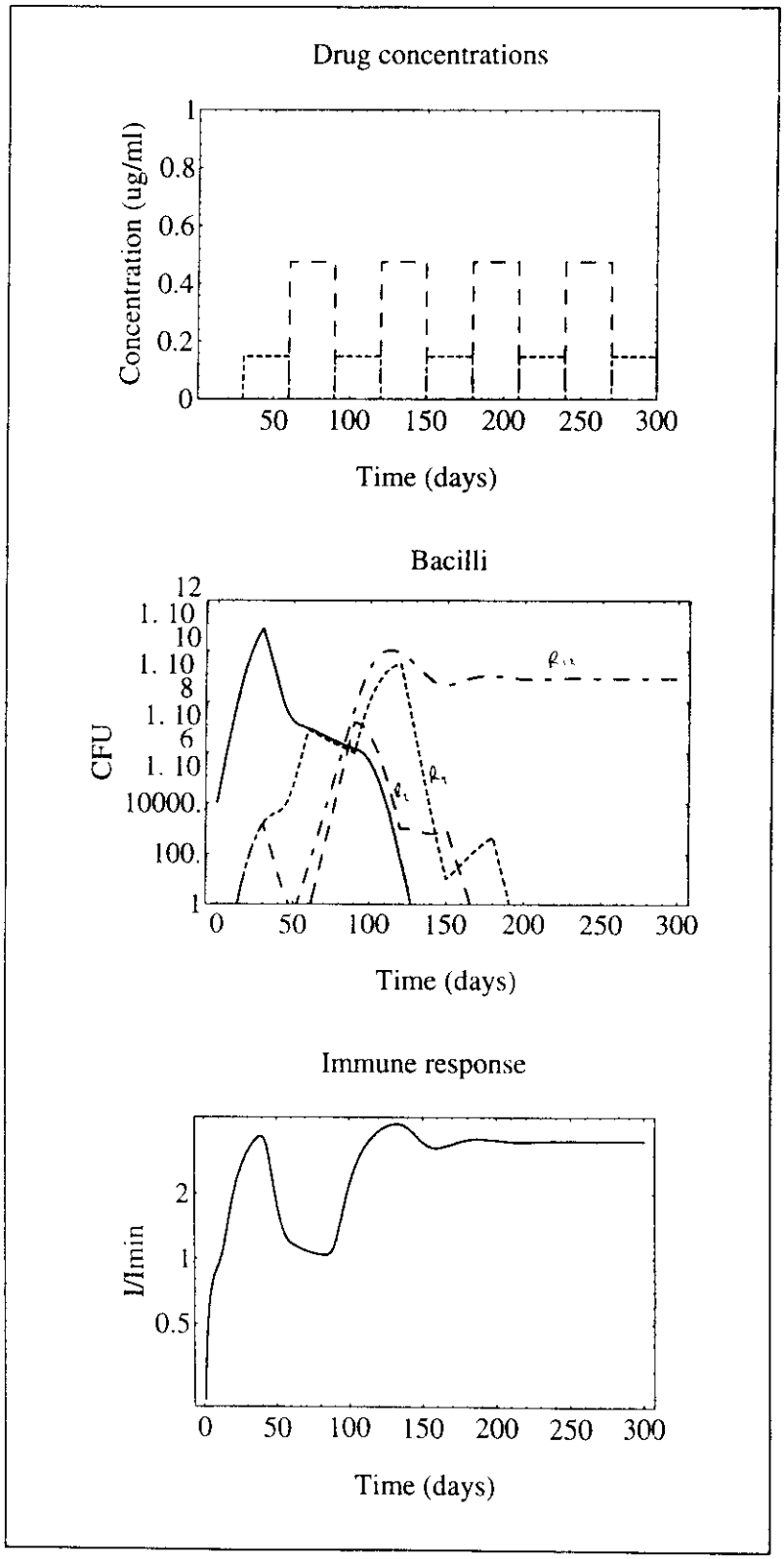
Continuous INH and Rifampin treatment



continuous dual therapy

Multiply Resistant

Alternate INH and Rifampin treatment



Medicated Treatment

Multiply Resistant