Optimal Use of Drug Supply during Pandemic Influenza

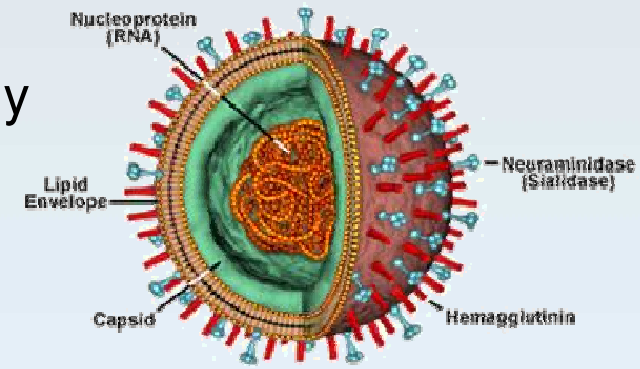
Seyed M. Moghadas

NRC-Institute for Biodiagnostics
and
The University of Winnipeg

MITACS-Fields Workshop
August 2008

Influenza: A Viral Disease

- Influenza is a respiratory disease
  - RNA viruses of the *Orthomyxoviridae* family



influenza viruses

A
(Hosts: humans, birds, non-primate mammals)

B
(Host: humans)

C
(Host: humans)

(strains)

H1N1 H2N2 H3N2 H5N1 H7N7 H9N2

Influenza **A** viruses responsible for the vast majority of epidemics and documented Pandemics

What is Pandemic?

- Global spread of disease with a new influenza viral strain
- What do we know?
  - pandemics will occur !
- What do we not know?
  - when it will occur; where it will originate; what virus will cause it
- 31 documented pandemics since 1580
- Pandemics of the last century:
  - 1918 (H1N1): Over 50 million deaths; Over 500 million infections
  - 1957 (H2N2): ~ 2 million deaths
  - 1968 (H3N2): ~ 1 million deaths
- Next pandemic: H5N1 (maybe … who knows?)

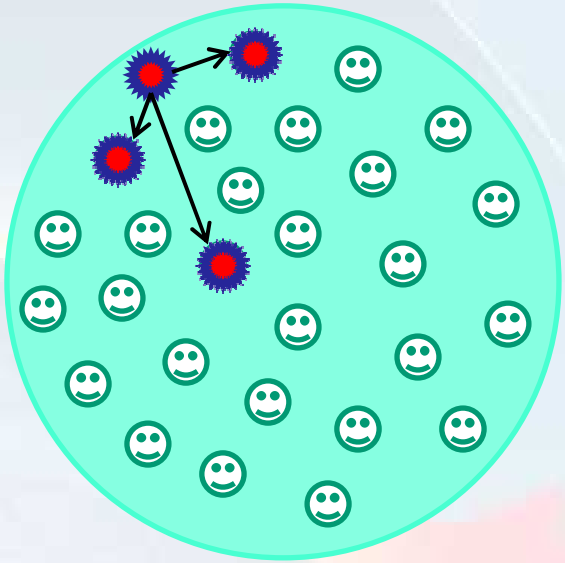
Control Strategies: Prevention and Treatment

- Non-pharmaceutical:
  - Isolation/quarantine (infectious/infected)
  - social distancing (school/border closure; travel restriction …)
  - personal protection (masks, gowns, gloves …)
- Severe Acute Respiratory Syndrome (SARS):
  - a modern example of containing a global epidemic through non-pharmaceutical public health interventions.
- Pharmaceutical:
  - vaccine (may not be available for newly emergent viruses)
    - **Limitation**: low efficacy; insufficient quantities; inadequate immune response
  - Antiviral drugs (prevention and treatment):
    - **Limitation**: inadequate supply; emergence of drug-resistance

Antiviral Therapy

- Antiviral drug use:
  - pre-exposure prophylaxis of susceptibles (prevention)
  - post-exposure prophylaxis of close contacts (prevention/treatment)
  - treatment of clinical infections
- Major threat to drug-use and effectiveness:
  - emergence of drug-resistance
- Competing issues in antiviral strategies:
  - minimizing the overall incidence of infection
    - requires aggressive treatment
  - preventing the spread of drug-resistance
    - avoid aggressive treatment
- Public Health Concern: strategic/optimal use of drugs
  - evaluating effectiveness of antiviral strategies: modelling approach

Disease Transmission in the Population



Susceptible

↓

Infected

↓

Removed

$$\frac{dS}{dt} = -\beta IS$$

$$\frac{dI}{dt} = \beta IS - \mu I$$

$$\frac{dR}{dt} = \mu I$$

- Basic Reproduction Number (R_0):
  - number of new infections produced by a single infected individual introduced into an entirely susceptible population

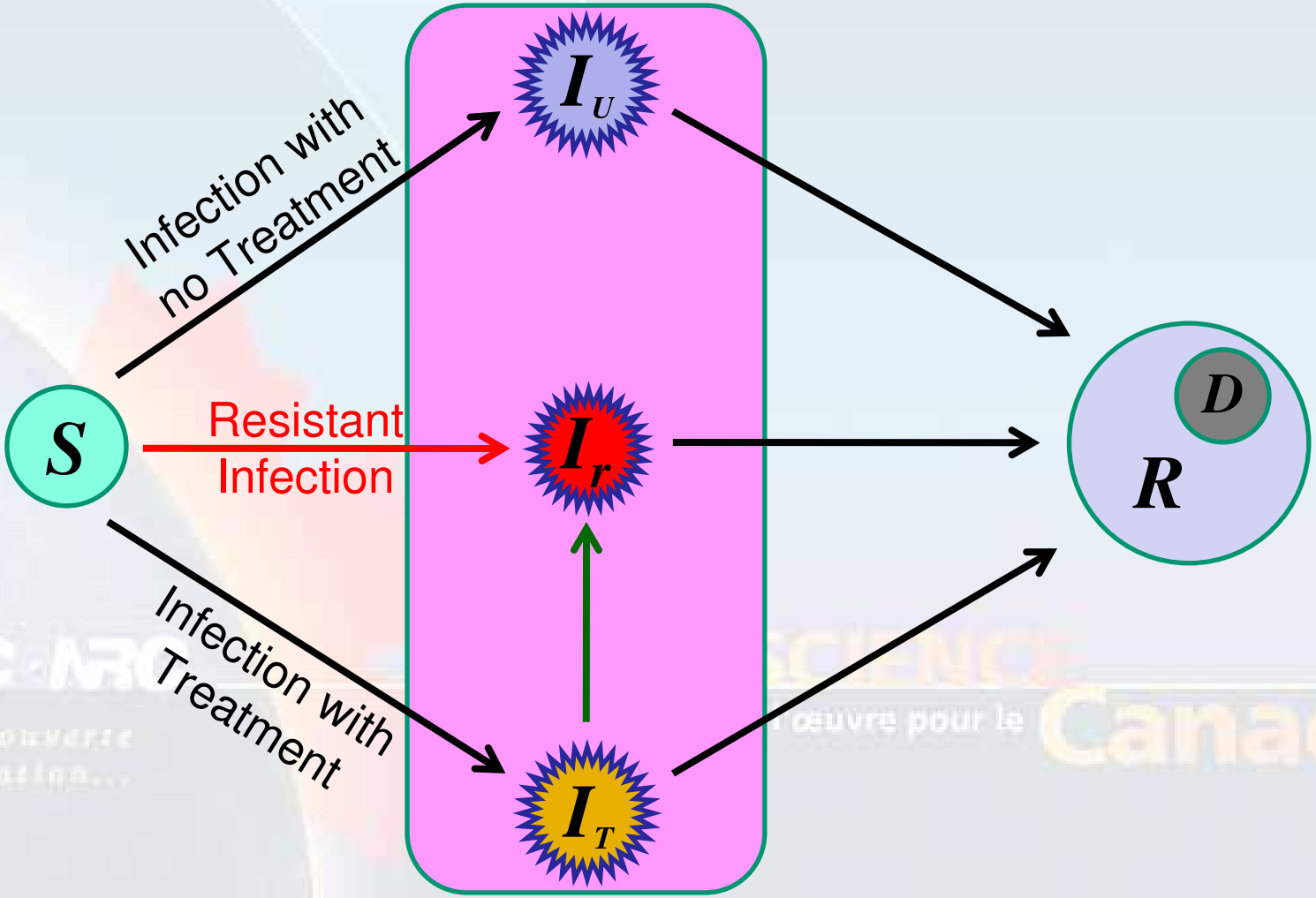
$$R_0 = \frac{\beta S_0}{\mu}$$

- R_0>1: disease spreads (epidemic)
- R_0<1: disease dies out (no epidemic)

R_0 for Previous Pandemics

	1918	1957	1968
Viboud et al. 2006, *Vaccine*	2.1	1.5	1.8
Gani et al. 2005, *Emerging Infectious Diseases*	2	1.7	2.2
Mills et al. 2004, *Nature*	2	—	—
Longini et al. 1986, *American Journal of Epidemiology*	—	—	1.9

SIR Model for Drug-Resistance



Model Equations

$$\frac{dS}{dt} = -\beta(I_U + \delta_T I_T + \delta_r I_r)S,$$

$$\frac{dI_U}{dt} = (1-p)\beta(I_U + \delta_T I_T)S - (d_U + \gamma_U)I_U,$$

$$\frac{dI_T}{dt} = p\beta(I_U + \delta_T I_T)S - (d_T + \gamma_T)I_T - \alpha_T I_T,$$

$$\frac{dI_r}{dt} = \delta_r \beta I_r S + \alpha_T I_T - (d_r + \gamma_r)I_r,$$

- Critical parameters:

p: treatment level

δ_T: drug-efficacy

α_T: rate of developing drug-resistance

δ_r: relative transmissibility of resistance

Various Treatment Strategies

- Constant treatment level throughout the epidemic
  - resistance can widely spread for high treatment levels

    Lipsitch et al, PLoS Medicine (2007)

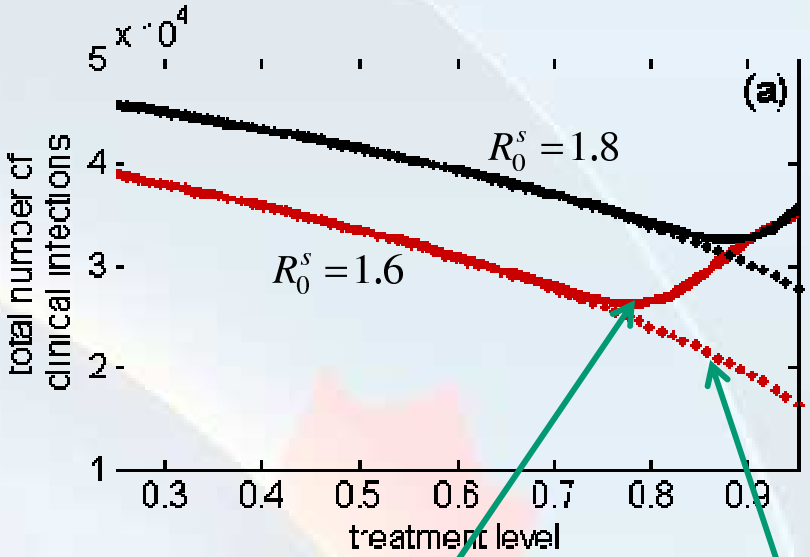
    Moghadas et al, PLoS ONE (2008)
- Variable treatment level:
  - High initial treatment levels followed by a reduction in antiviral use
  - poor strategy in control of resistance

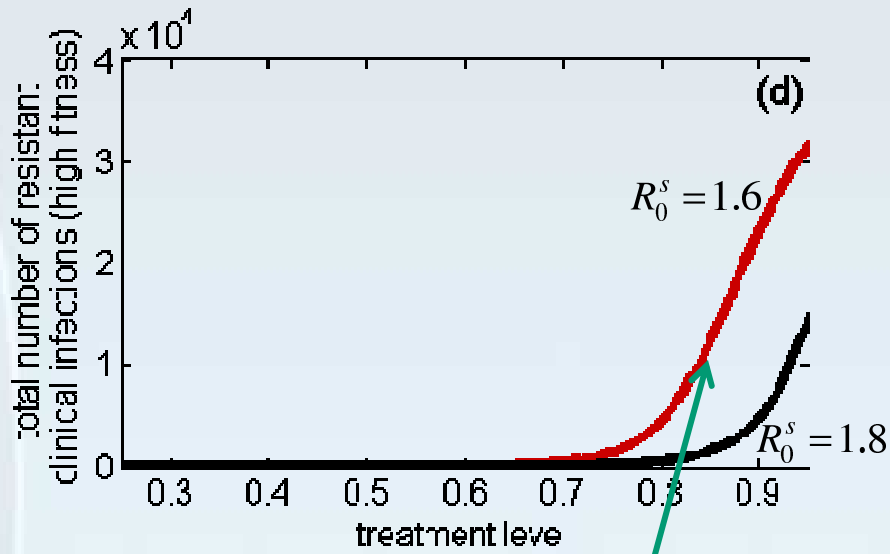
    Ferguson et al, Nature (2005)
  - Adaptive treatment strategy:
  - low initial treatment levels followed by a timely intensive treatment
  - Prevent resistance spread and reduce the overall infections

    Moghadas et al, PLoS ONE (2008)

    Moghadas, Proc. R. Soc. B (2008)

Constant Treatment Strategy



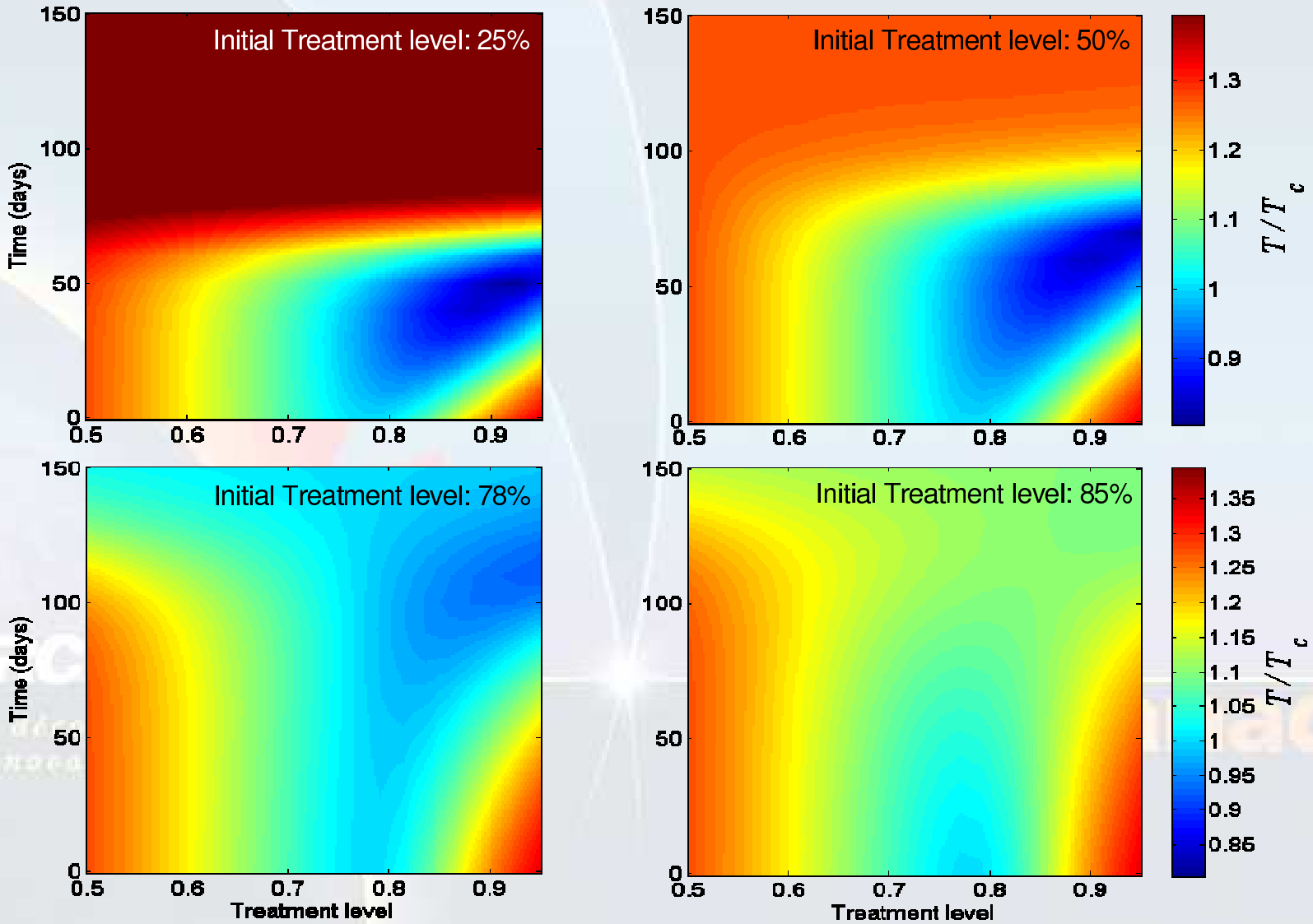


minimum infections
(in the presence of resistance)

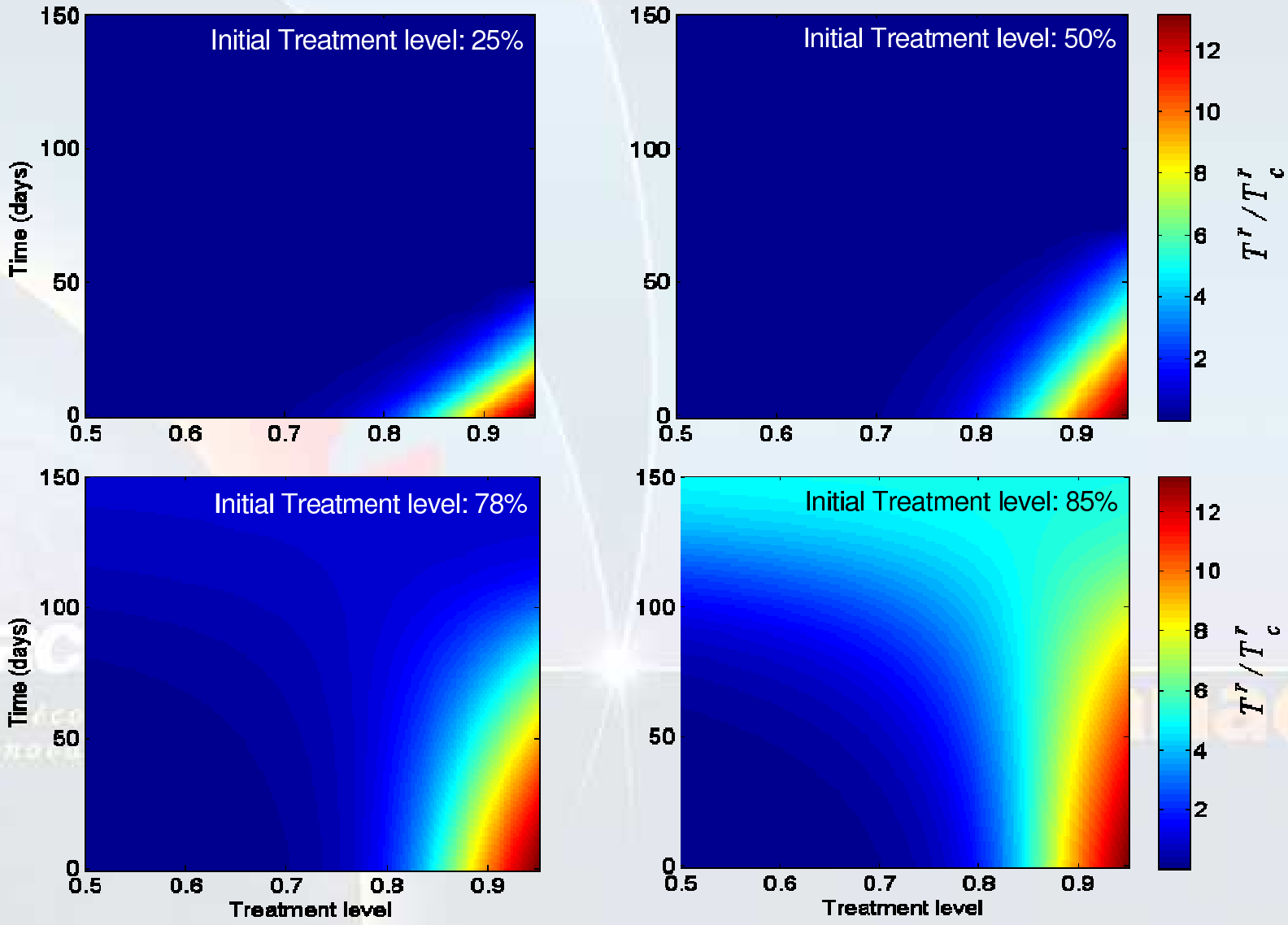
spread of resistance
for high treatment levels

reduction in total infections
(in the absence of resistance)

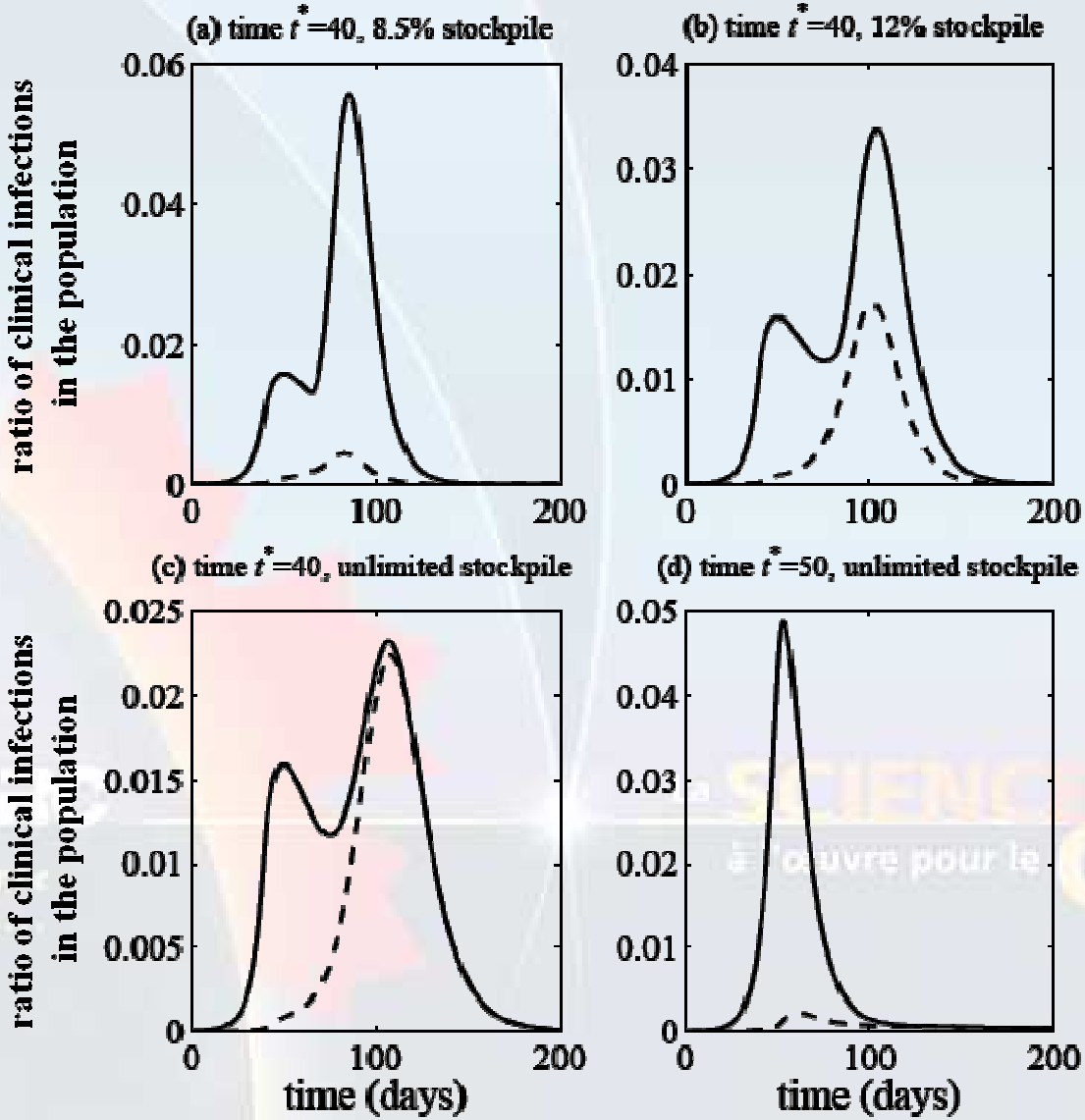
Adaptive Treatment Strategy: Total Infection



Adaptive Treatment Strategy: Resistance



Limited Stockpile: Consequences of Run-Out



Problems

- Assumptions:
  - emergence of resistance
  - stockpile is limited and run-out is likely to occur
- Find the optimal treatment strategy to:
  - minimize disease burden
  - prevent the spread of resistance
  - adjust policy according to emerging information
- What is the best modelling approach?
  - determinism versus stochasticity
  - identify key parameters of the model
  - validating the model and its predictions

Acknowledgements

- Collaboration with:

  Alexander ME; Bowman CS (NRC-Institute for Biodiagnostics)
  Arino J; Hua Y (University of Manitoba)
  Brauer F (University of British Columbia)
  Feng Z (Purdue University)
  Gardam M (University Health Network)
  Liang D; Wu J; Zeng Q; Zhu H (York University)
  Röst G (University of Szeged)
  van den Driessche P (University of Victoria)
  Watmough J (University of New Brunswick)
  Yan P (Public Health Agency of Canada)

- Financial Support:

  MITACS; MOHLTC; NSERC; CRCP; OTKA; PHAC