2/4/2015
Ebola Modeling Call
Organizer: Kun Hu, IBM

Limits to Confidence in Estimates of R_0 as Inferred from EVD Case Data

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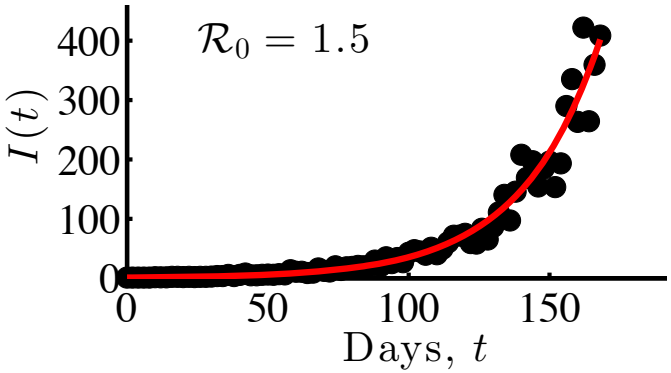
BURROUGHS WELLCOME FUND


$\mathcal{R}_0 = 1.5$
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$I(t)$
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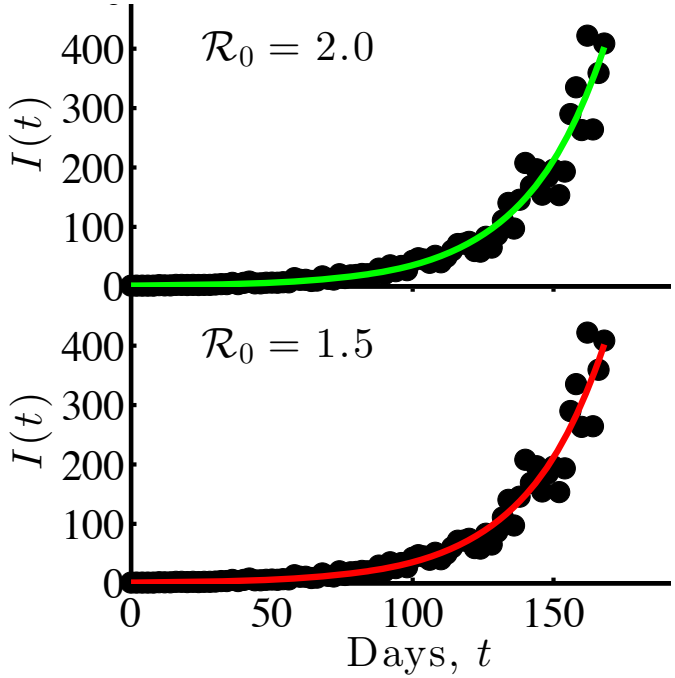
Days, t


$\mathcal{R}_0 = 2.0$
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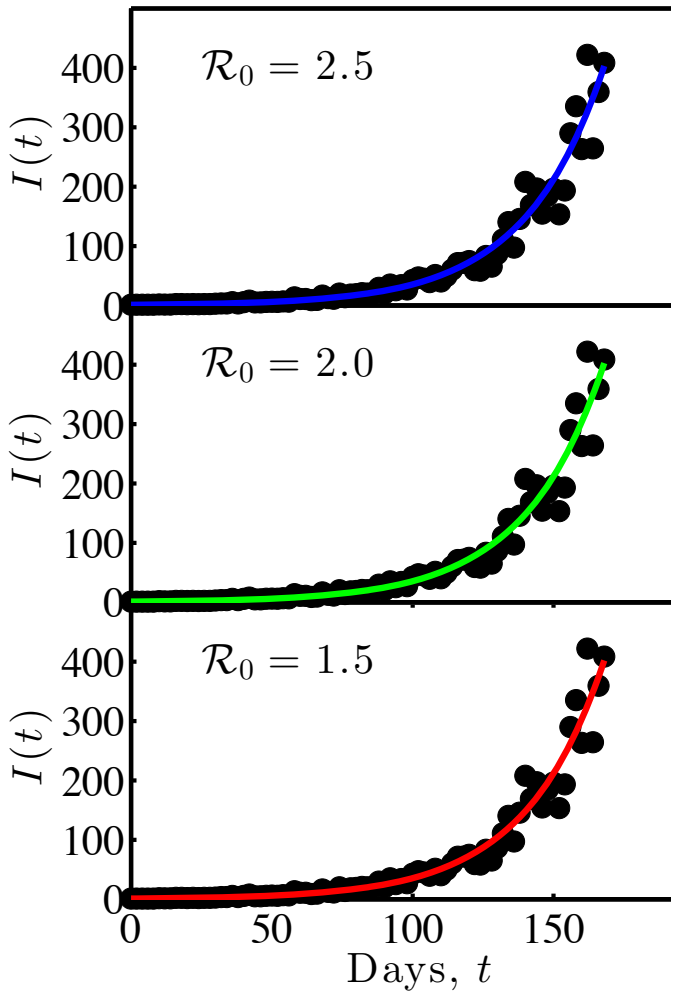
$\mathcal{R}_0 = 2.5$
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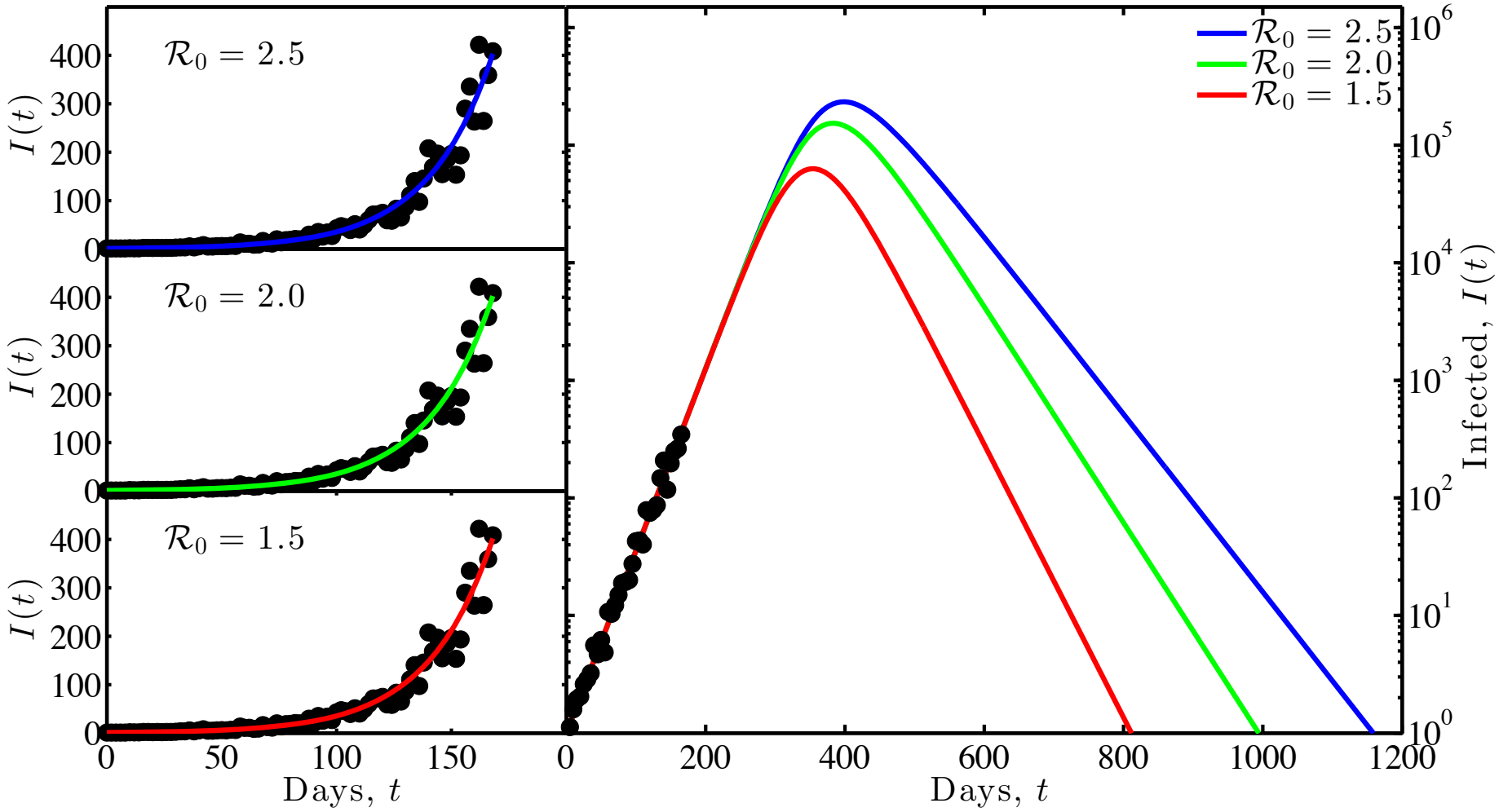
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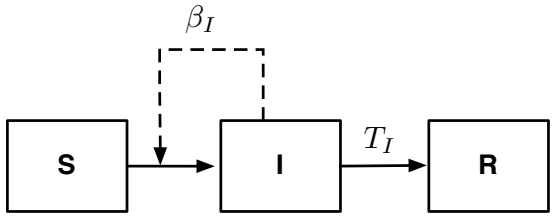
Infected, $I(t)$

SIR Model – Initial Dynamics



The number of cases at any given time grows like*:

$$i(t) = i_0 e^{\lambda t}$$

*The same growth rate holds for the cumulative number of cases.

where

$$\lambda = (\mathcal{R}_0 - 1)/T_I$$

In practice, an estimate of the epidemic growth rate λ can be used to infer the unknown value of $\mathcal{R}_0$.

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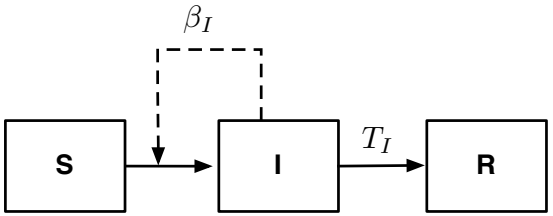

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Yet: many combinations of infectious period and the basic reproductive number yield the same apparent growth rate (previous slides used synthetic data to illustrate this point).

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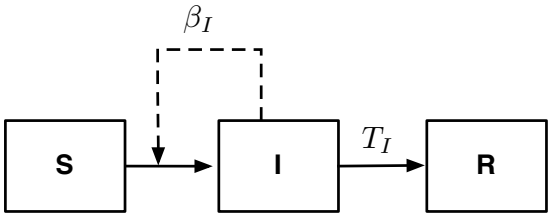

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This is called an "identifiability problem" (see Keeling & Rohani, 2007)

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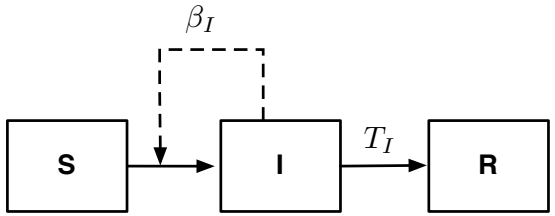

Question: consider data on an epidemic in which λ = 1/4 weeks where

Disease 1: T_I = 1 week

Disease 2: T_I = 4 weeks

Which disease has the higher $\mathcal{R}_0$?

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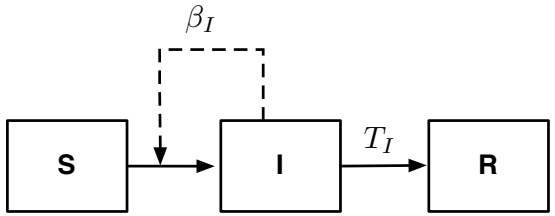

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Answer: Disease 2

Algebra: $\mathcal{R}_0 = 1 + T_I \lambda$

Disease 1: $\mathcal{R}_0$ = 1.25

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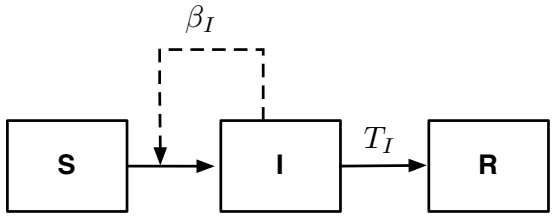

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Intuition:

Disease 1 takes 4 infectious periods to "double" the case count.

Disease 2 takes only 1 infectious period to "double" the case count.

Hence, disease 2 has a higher average number of secondary infections per average infectious period (the definition of $\mathcal{R}_0$).

Given observations of case data from an epidemic:

- Multiple models can equally "fit".
- These models may differ in their underlying mechanisms, including the basic reproductive number.
- Despite equivalent early-dynamics, the consequences can be very different at later times and for control.

Today:

Inferring the basic reproductive number from epidemic data, with applications to the Ebola epidemic in West Africa.

Part 1 of 2: Uncertainty in estimating R_0 arising from uncertainty in the timing of infectious events, pre- and post-death.

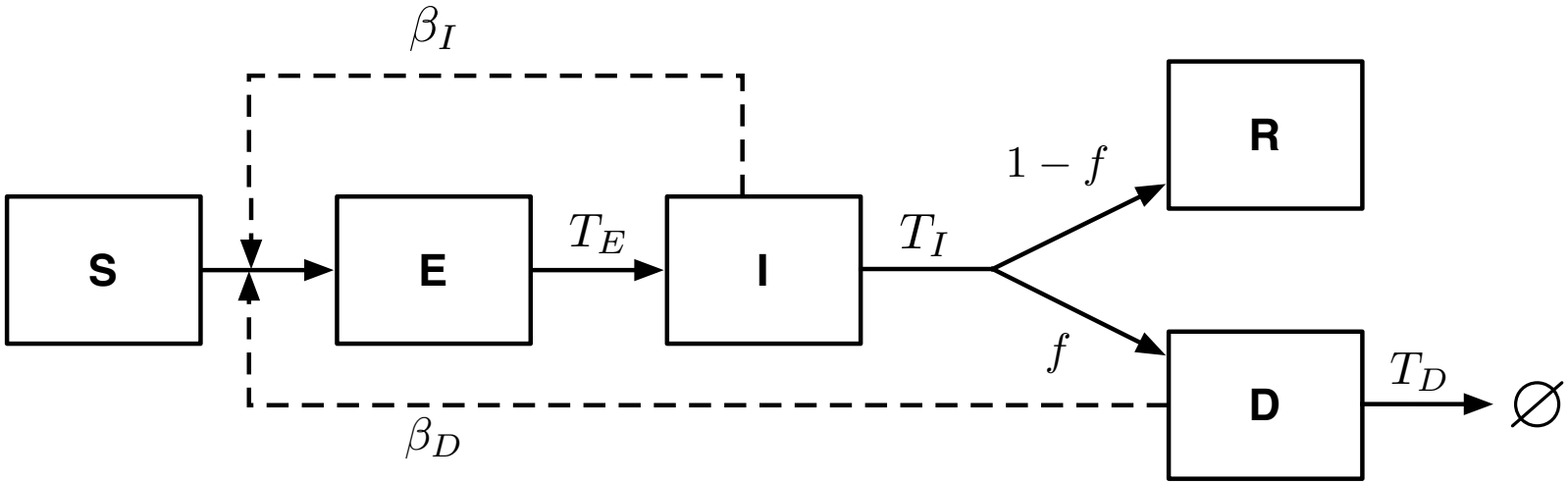
Focus today

Part 2 of 2: Uncertainty in estimating R_0 arising from the discrete transmission process.

Future topic?

SEIR-D Model of Ebola Dynamics

A subset of recent models (e.g.,; Lewnard et al., Lanc. Inf. Dis. 2014; Gomes et al., PLoS Curr Outbreaks, 2014; Pandey et al., Sci 2014, Weitz & Dushoff, Sci Rep, 2015, in press)



Working Assumptions: Same as SEIR model, except:

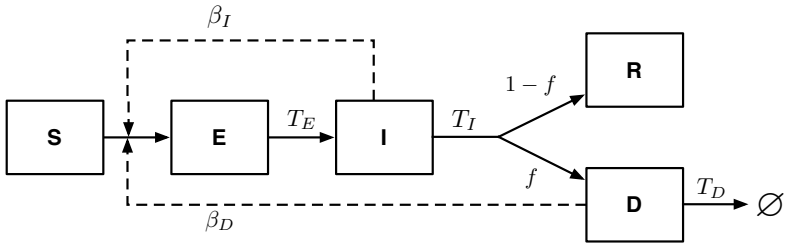
A fraction 1-f of infected individuals recover and are moved into the *R* class.

A fraction f of infected individuals die and are moved into the *D* class.

Dead (but as yet unburied) individuals can transmit disease to *S* individuals.

Dead individuals are buried with a characteristic time T_D

SEIR-D Model



Consider an SEIR-D model in which

Latent period: T_E = 11 days
Infectious period: T_I = 6 days
Probability of death: f = 0.7

Given a characteristic time of ~3 weeks for the spread of disease…

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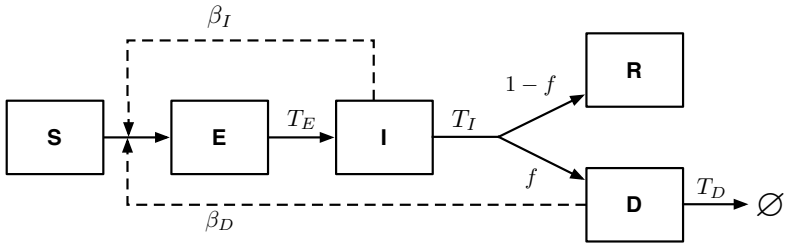

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β_I β_D T_D

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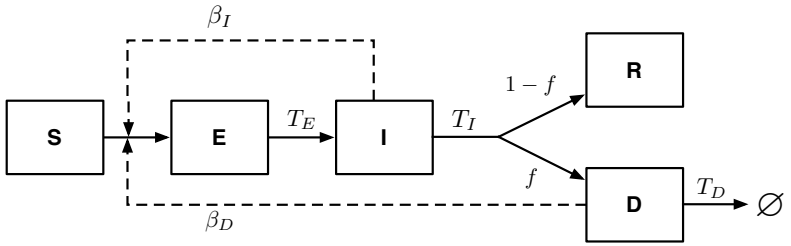

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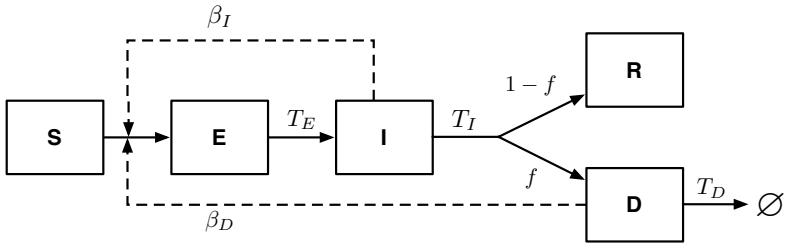
What combinations of parameters yield the same epidemic growth rate?

Generating function formalism



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$$M(z) = \int_0^\infty e^{za} g(a) \mathrm{d}a$$

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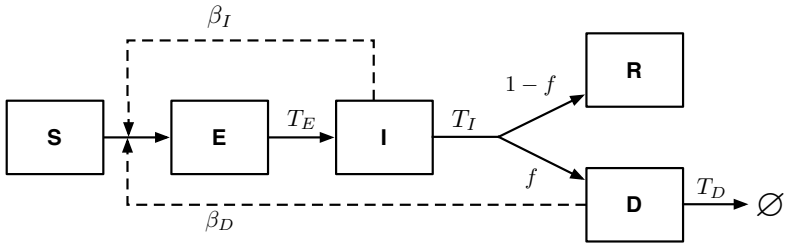

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For the SEIRD model:

$$M(z) = (1-\rho_D) M_E(z) M_I(z) + \rho_D M_E(z) M_I(z) M_D(z)$$

$$M_E(-\lambda) = \left(\frac{b_E}{b_E+\lambda}\right)^{n_E}$$

$$M_I(-\lambda) = \frac{\gamma}{\gamma+\lambda}$$

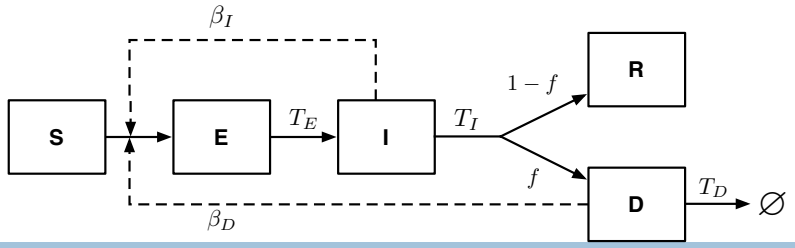
$$M_D(-\lambda) = \frac{\chi}{\chi+\lambda}$$

Here, as derived for a gamma distribution for exposed period.

Exponential distributions for

- Infectious period
- dead period

SEIR-D model dynamics



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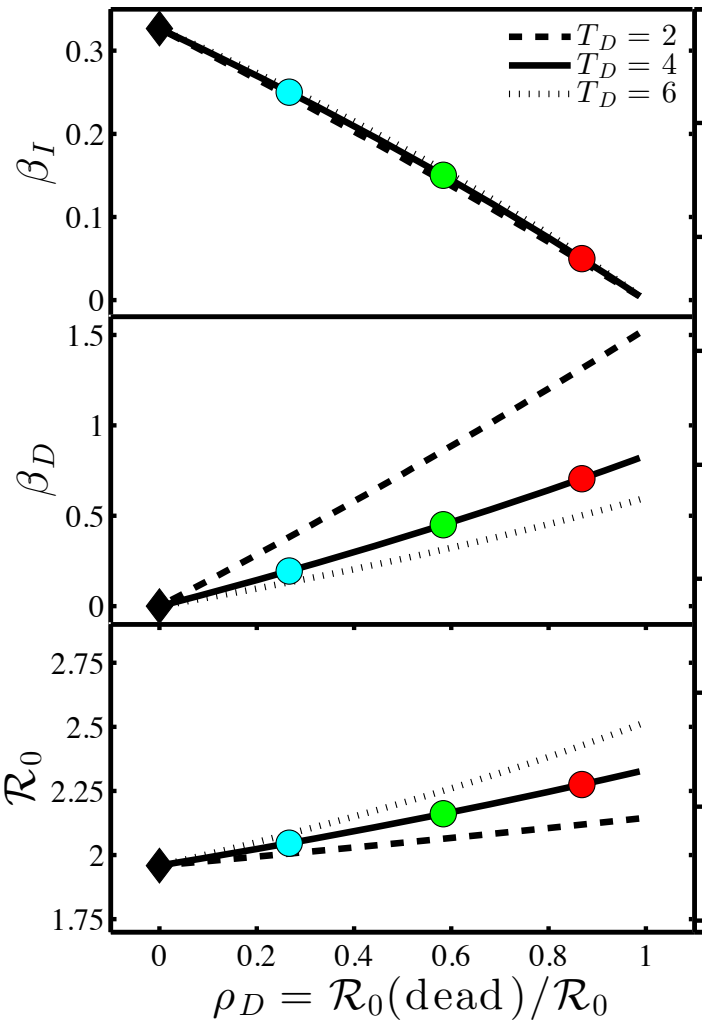
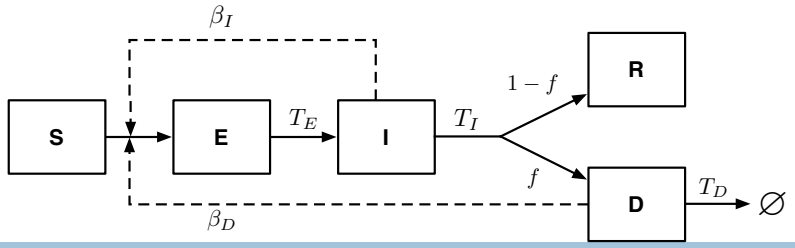
Multiple "scenarios" ●, ●, and ● all yield the same predicted epidemic growth rate (using next-generation matrix approach or similar methods).



SEIR-D model dynamics



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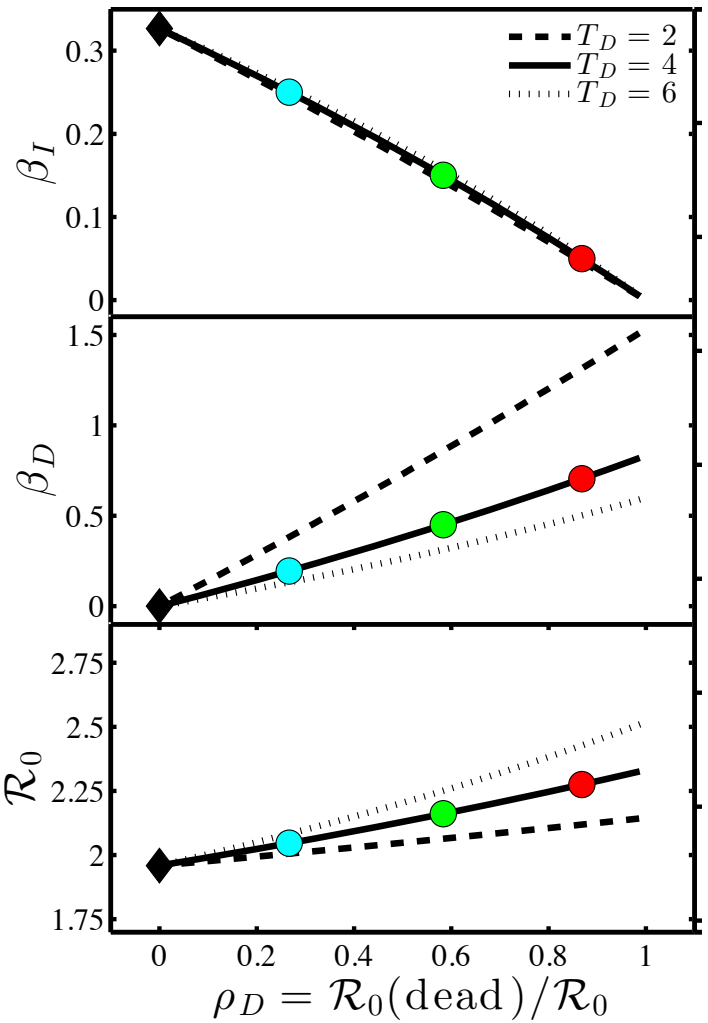
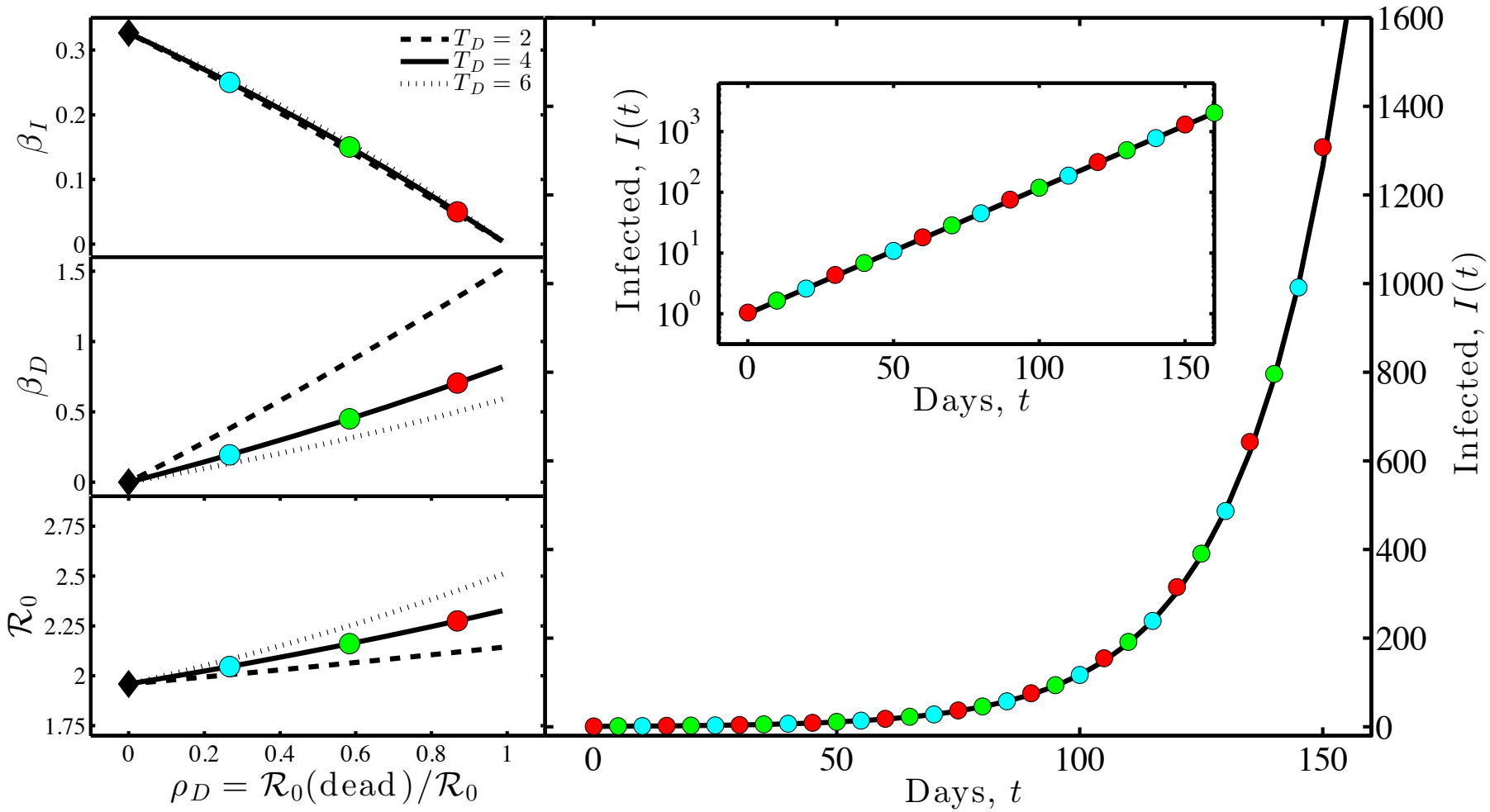
These "scenarios" ●, ●, and ● all have a higher R_0 due to post-death transmission when compared to a SEIR model prediction.



SEIR-D model dynamics

Weitz & Dushoff (Sci Reports, in press), arXiv:1411.3435



On extending the model when recovery times differ from time to death

Q1. What is the potential affect of changes in the time to death vs. the time recovery have on the present analysis?

Rationale: Time to recovery can be on the order of 12-16 days whereas time to death is only 6 days.

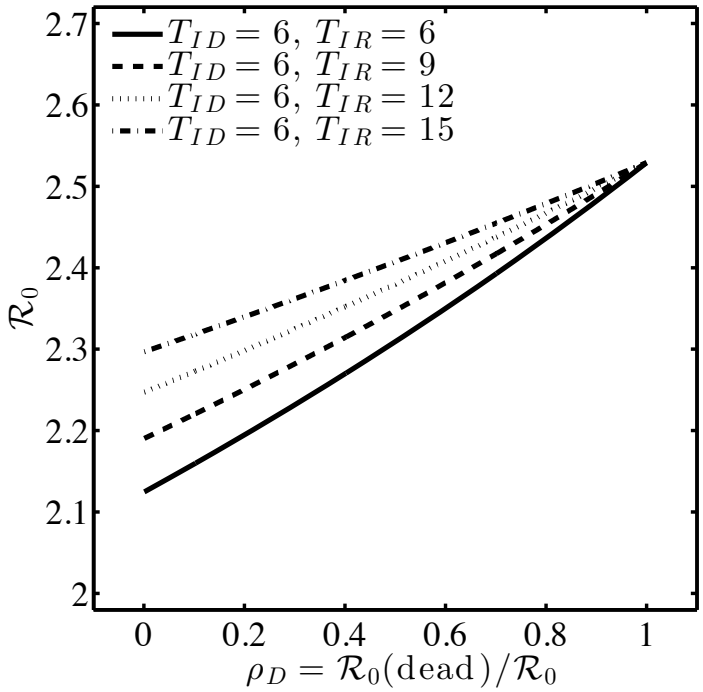
On extending the model when recovery times differ from time to death

Q1. What is the potential affect of changes in the time to death vs. the time recovery have on the present analysis?

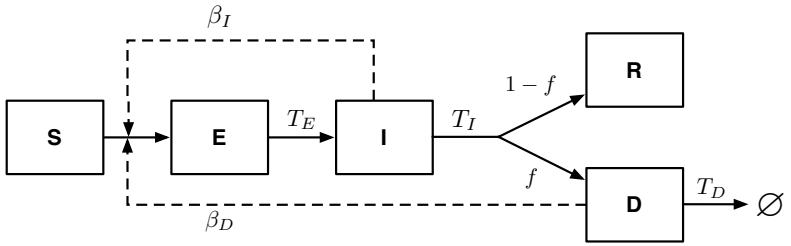
Rationale: Time to recovery can be on the order of 12-16 days whereas time to death is only 6 days.

Answer: Increasing post-death transmission leads to increases in estimates of R0.

Follow-up: investigate the hazard of transmission during recovery and leading up until death (unlikely to be constant).



SEIR-D Model



SEIR-D model requires information on:

- Duration of the latent period
- Duration and infectivity of infectious individuals
- Duration and infectivity of dead, but still infectious, individuals.

Assume, for now, latent period is gamma-like, but that the infectious and dead periods are exponential-like (can easily be adapted using the method).

How well can a SEIR-D model "fit" the early exponential increase in EVD cases?

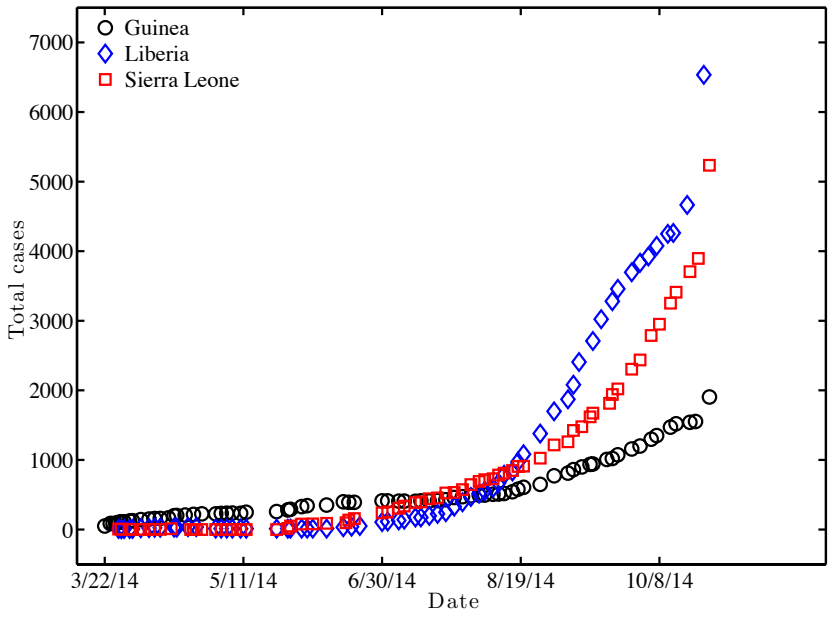
Data source:

Caitlin Rivers' public datasets:
https://github.com/cmrivers/ebola

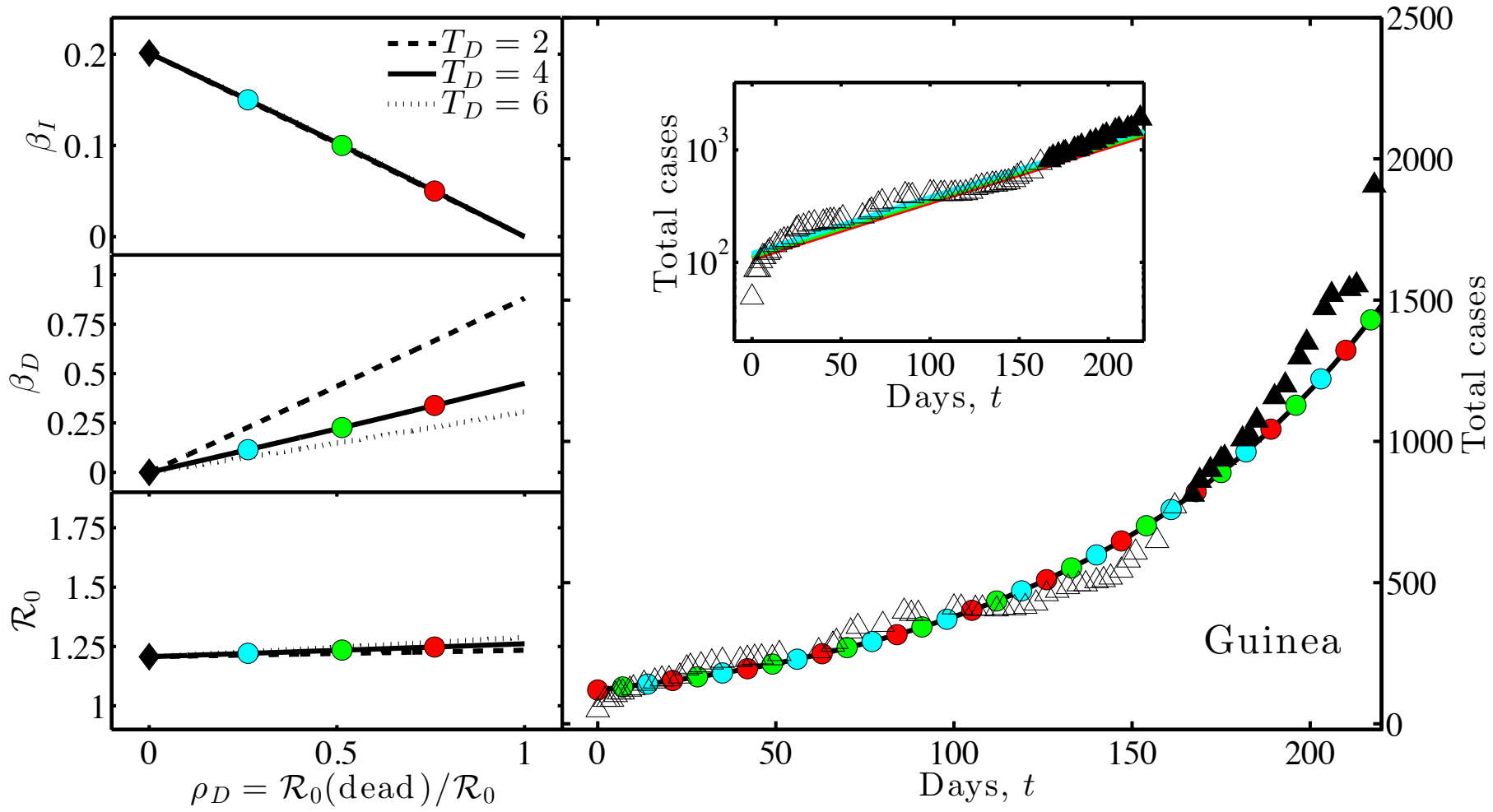
Guinea
Liberia
Sierra Leone

Method

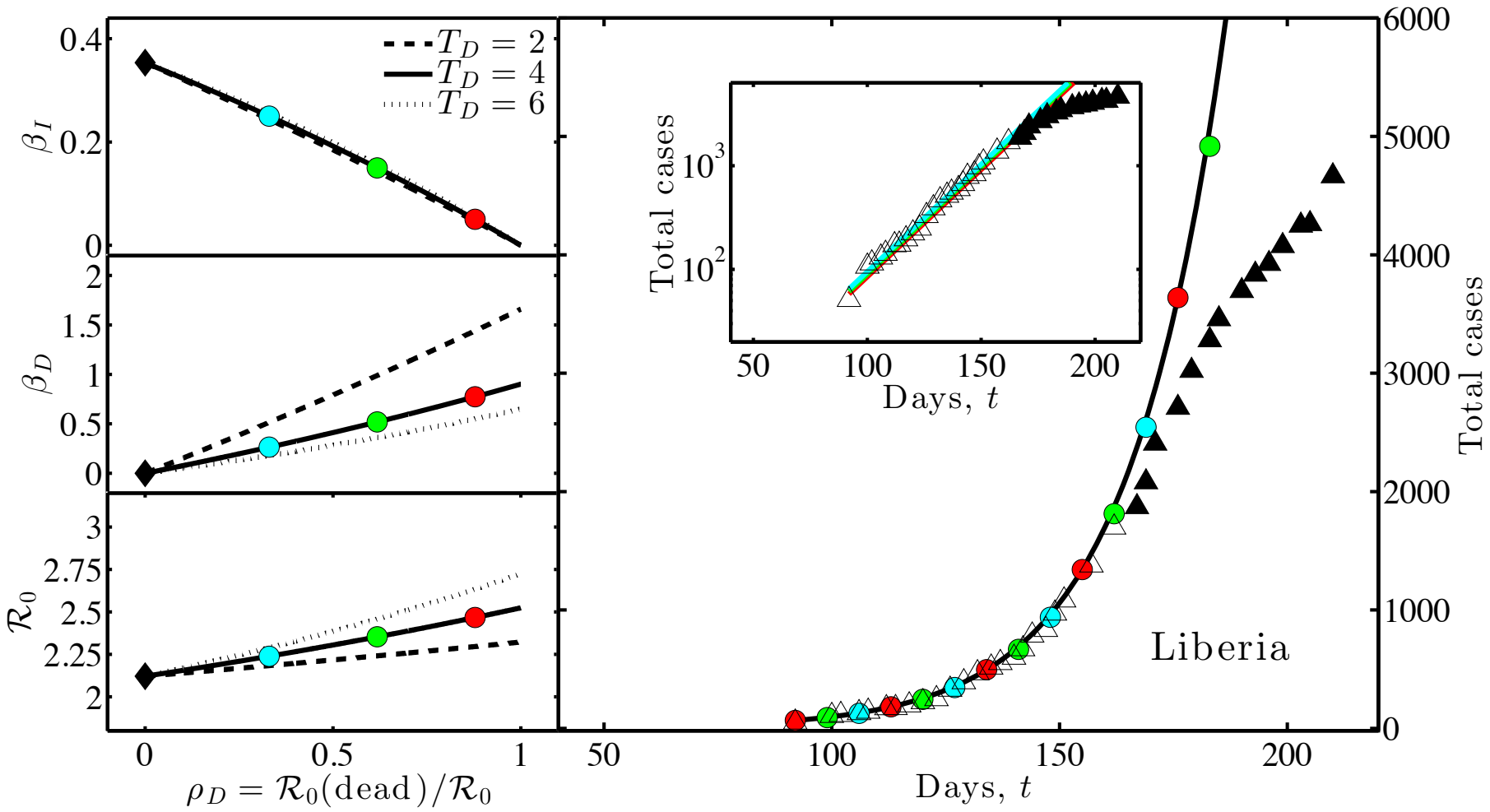
Adapted the generating function approach of Wallinga and Lipsitch (PRSB, 2007)



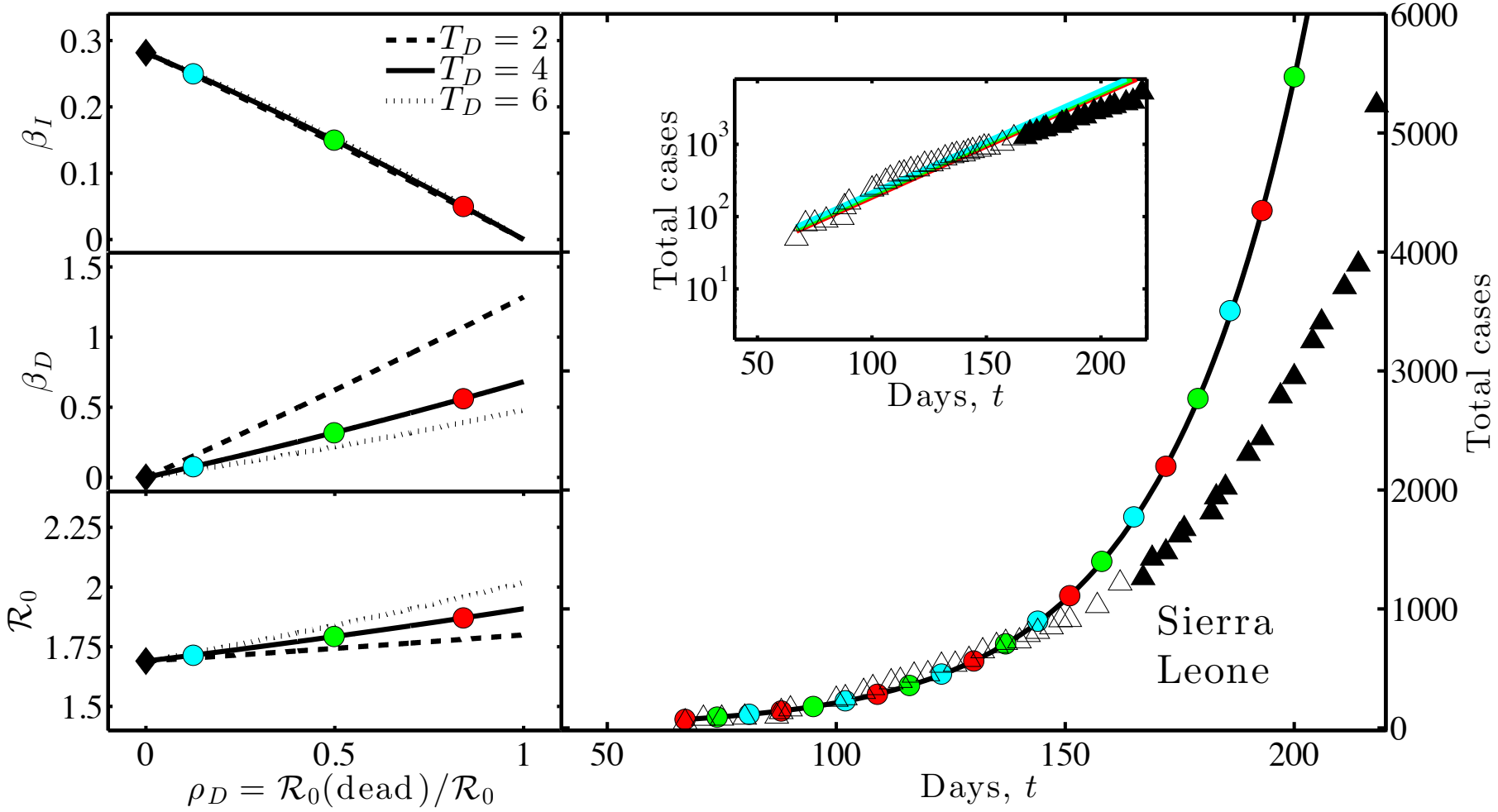
Model fits to case data: Guinea



Model fits to case data: Liberia



Model fits to case data: Sierra Leone



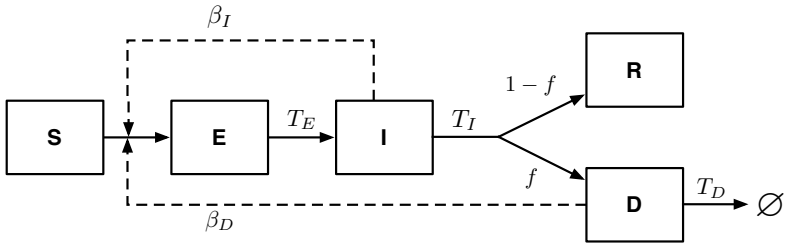
Uncertainty in R_0 for each country due to identifiability problem based on SEIRD fits

Country	R_0 (10% post-death transmission)	R_0 (40% post-death transmission)
Guinea	1.22	1.24
Liberia	2.20	2.33
Sierra Leone	1.70	1.81

Point of interest: The uncertainty in R_0 arising from uncertainty in chains of transmission may approach or even exceed that from fitting a given dynamical model to case data.

Note: many early fits of EVD case data had very narrow CIs.

SEIR-D Model



Take-home messages:

Multiple "scenarios" ●, ●, and ● all yield the same predicted epidemic growth rate.

For a given growth rate, a larger proportion of post-death transmission implies a larger value of R_0.

Optimistically, the effect on R_0 is modest, generally <10%, so long as post-death transmission is relatively short in duration compared to total period.

Strategies and Thoughts Related to Post-Death Transmission of Ebola

Contact-tracing of ~700 cases suggests that between 10%-30% of transmissions are due to transmission via contact with dead individuals (see WHO-NEJM, SI).

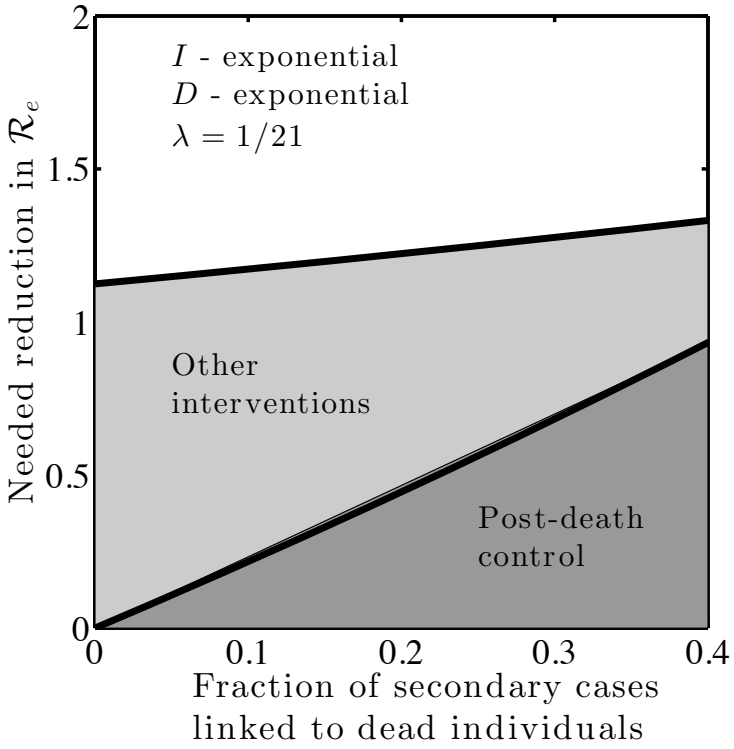
Post-death transmission implies a longer "effective" infectious period and, in turn, a modestly larger value of R_0.

But, improvements in burial practice may also lead to substantial reductions in R_0 via:

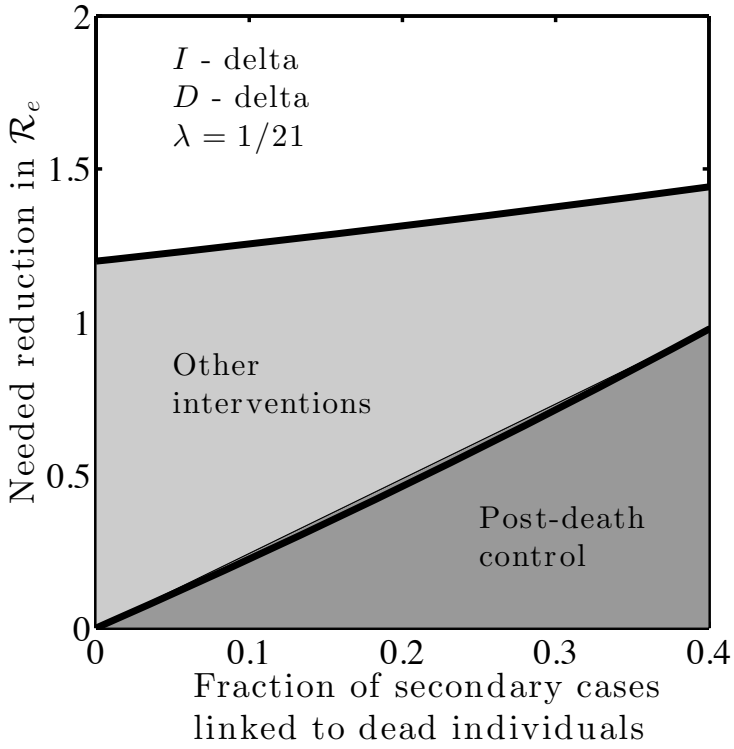
- Reduction in post-death transmission rate
- Reduction in delay to burial

Benefits of Control of Post-death transmission (before/during burials)

Case 1: Infectious (I) and dead (D) periods are exponentially distributed & 3 week characteristic growth rate.



Case 2: Infectious and (I) and dead (D) periods are peaked & 3 week characteristic growth rate.



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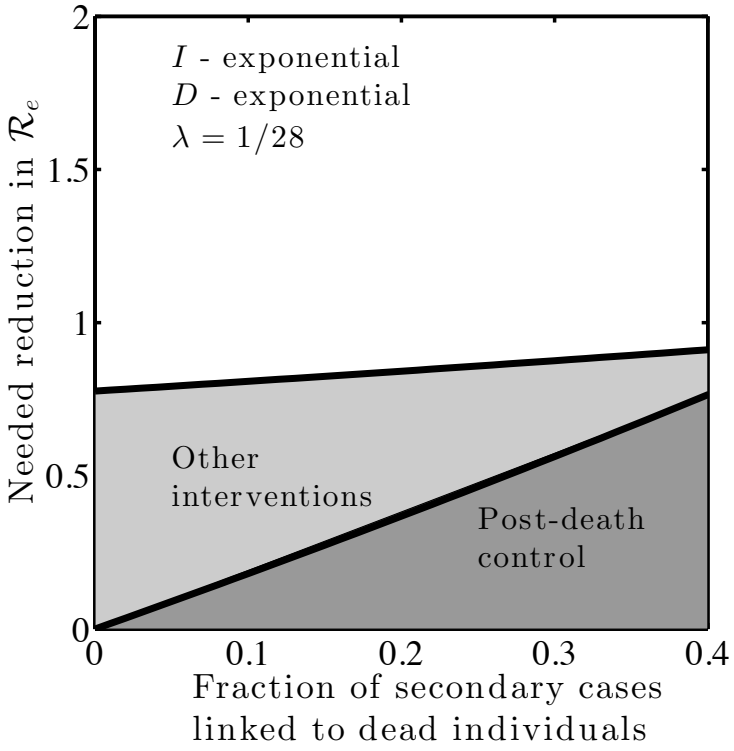

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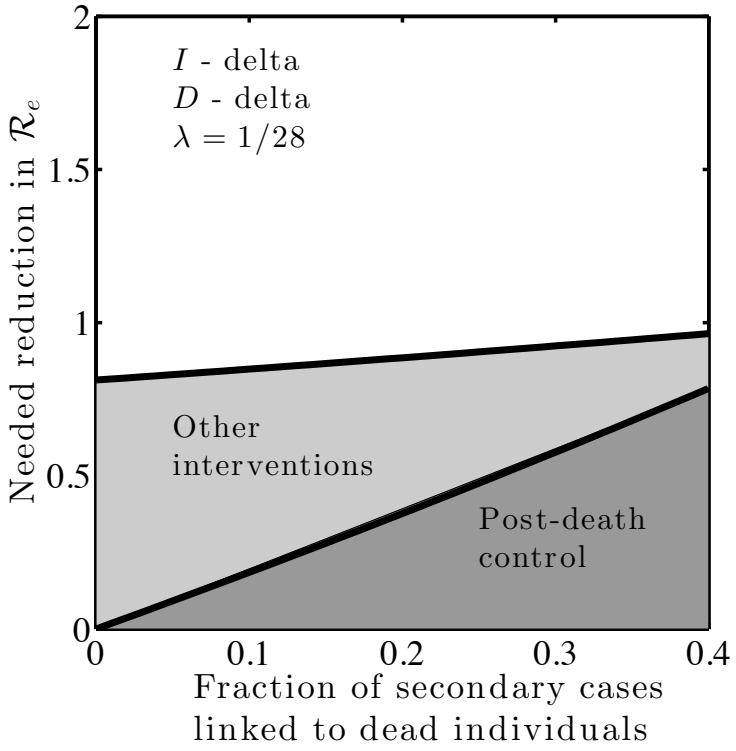


Summary of analysis of post-death transmission of Ebola

Take-home message 1:
Estimates of R_0 for Ebola that focus on transmission while alive will necessarily be under-estimates, when inferences are made given the same epidemic growth data.

Take-home message 2:
Reduction of post-death transmission of Ebola may be substantial (e.g., one-half) of the necessary reduction in secondary transmission to stop epidemic spread (drop R_e below 1).

Take-home message 3:
Uncertainty in the "age"-dependent hazard is a barrier to estimates of R_0 given case data. Hazard is unlikely to be constant!

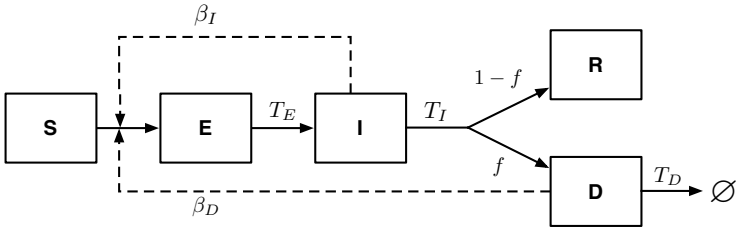
Part 1 of 2: Uncertainty in estimating R_0 arising from uncertainty in the timing of infectious events, pre- and post-death.

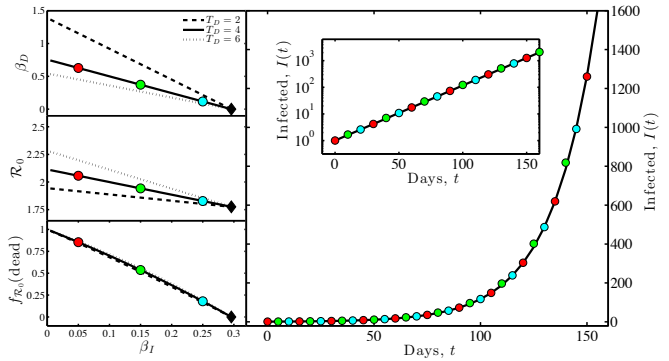
Weitz & Dushoff (in press) Scientific Reports & arXiv:1411.3435

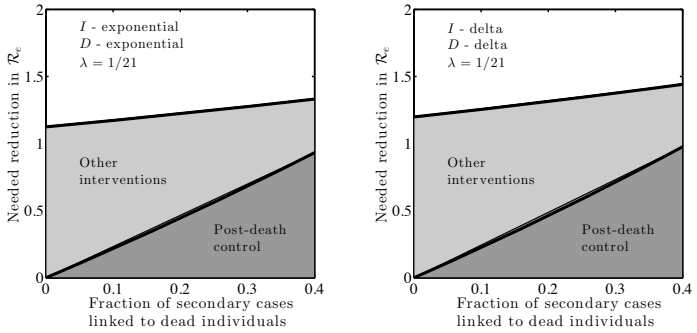
Part 2 of 2: Uncertainty in estimating R_0 arising from the discrete transmission process.

Future topic?

Questions?







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