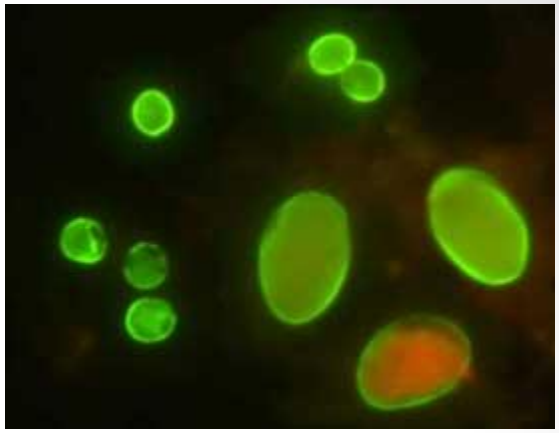
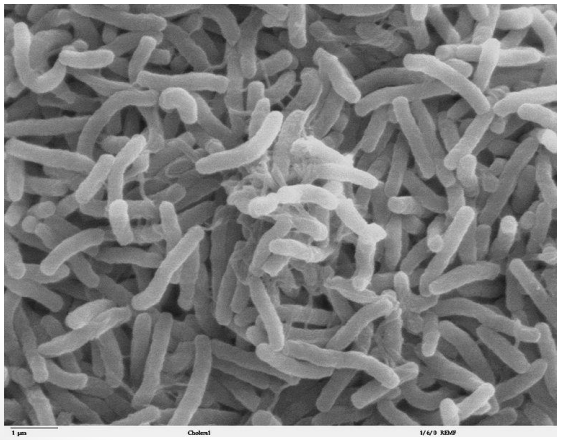
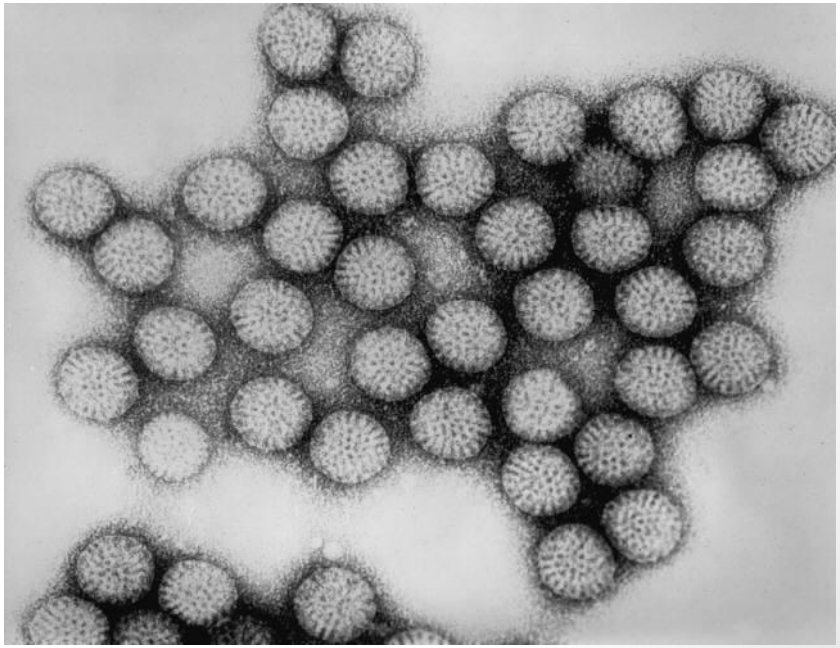


Dose–response relationships for transmission modeling

Andrew Brouwer

University of Michigan





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  - Joseph Eisenberg, University of Michigan
  - Mark Weir, The Ohio State University
  - Marisa Eisenberg, University of Michigan
  - Rafael Meza, University of Michigan

The role of the environment

- Historically, classical SIR dynamics, which do not explicitly model the environment, have been very successful at modeling outbreaks.

- However, the environment mediates transmission for many pathogens, which can impact dynamics. This occurs in a variety of media: water, air, food, fomites, etc.

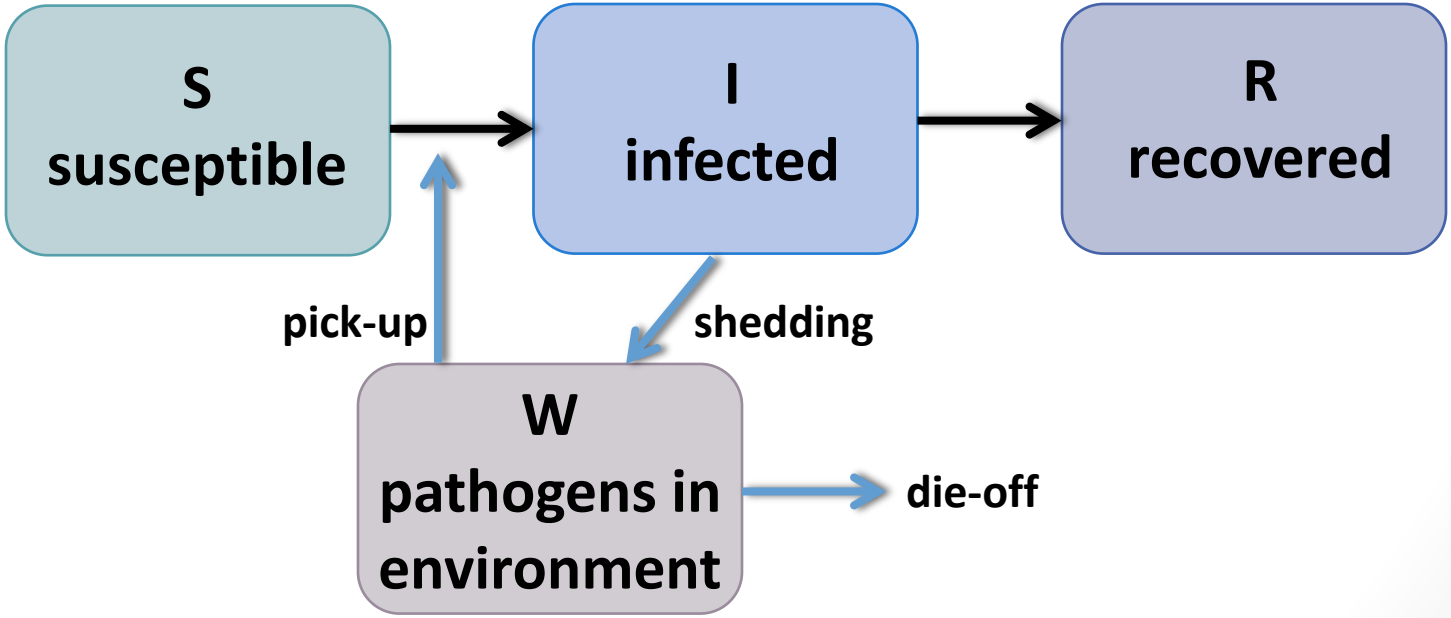
The role of the environment

- Mitigation often uses environmental interventions: water treatment, hand-washing, surface decontamination, etc.

- Explicitly modeling the environment allows us to consider environmental interventions, pathogen persistence and transport, and the variability of pathogen dose.

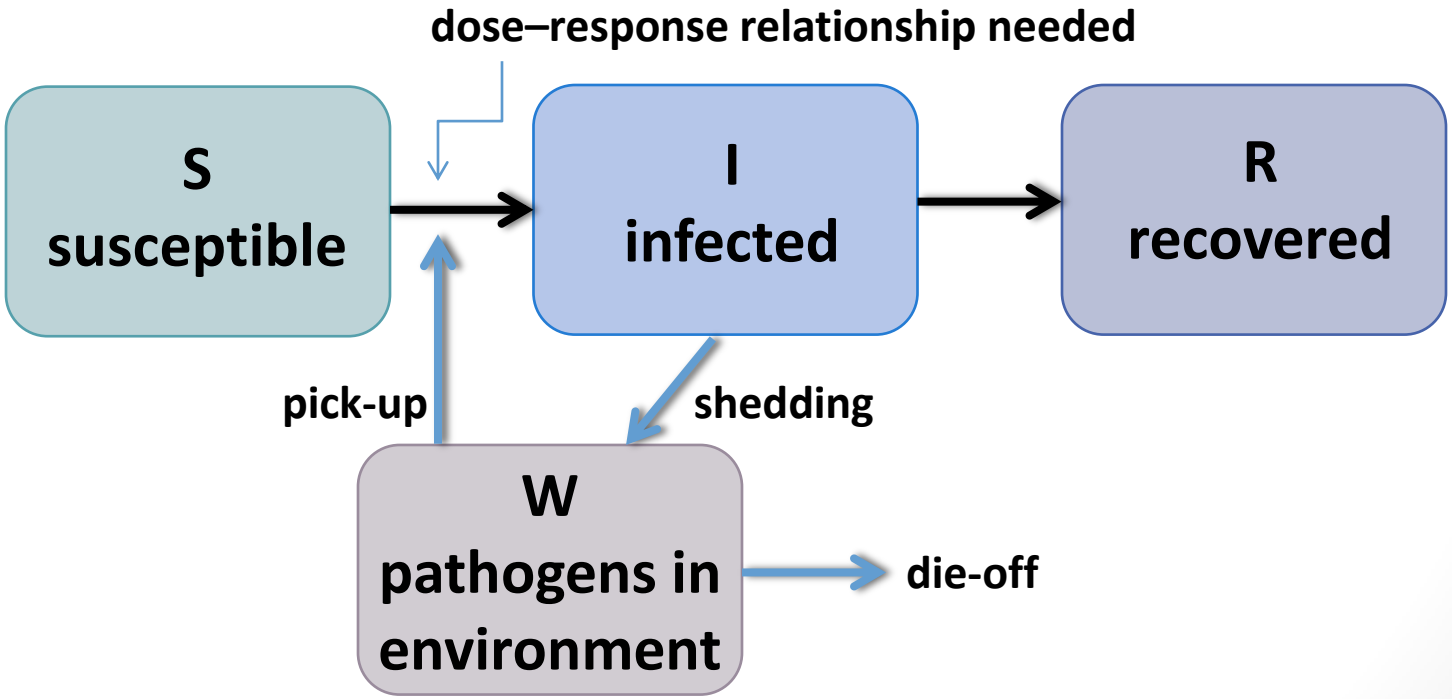
Framework

- EITS (Li, 2009) and SIWR (Tien and Earn, 2010) are two models that explicitly considers the role of the environment.



Framework

- We need to model the relationship between the number of pathogens someone is exposed to and the corresponding probability of infection



Dose-response relationship

- The probability of becoming infected may not be linear with pathogen dose.
- Categories of DR functions
  - Biologically derived: exponential, exact beta-Poisson
  - Mathematically convenient: Hill functions, linear, approximate Beta-Poisson
  - Empirically derived: log-normal, Weibull

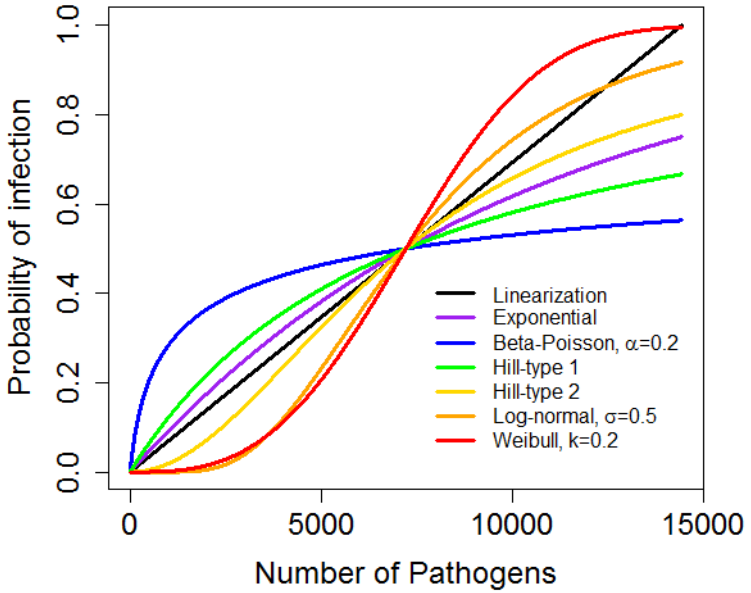


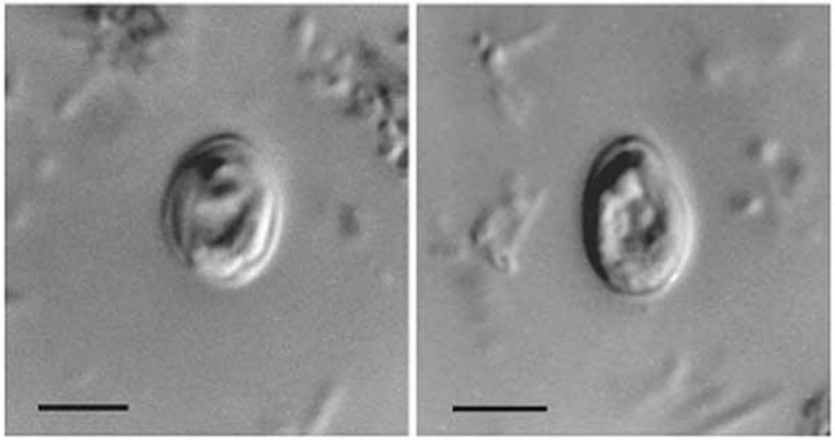
Figure: Example DR functions, with same ID_{50}.

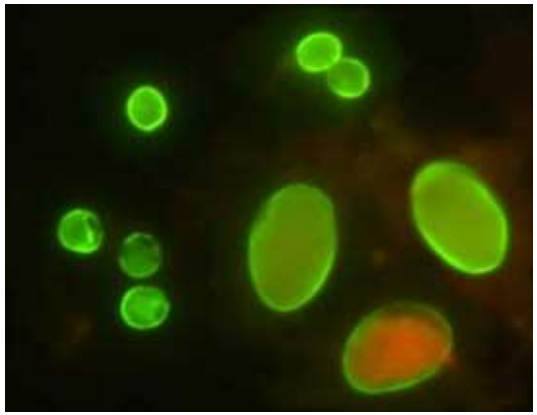
State of the field

- The field of quantitative microbial risk assessment (QMRA) has developed much the experimental dose–response literature.
- Theoretical work for ODE transmission models has been agnostic to functional form.
- Implications of the choice of dose–response functional form have not previously been described.

Example: *Cryptosporidium*

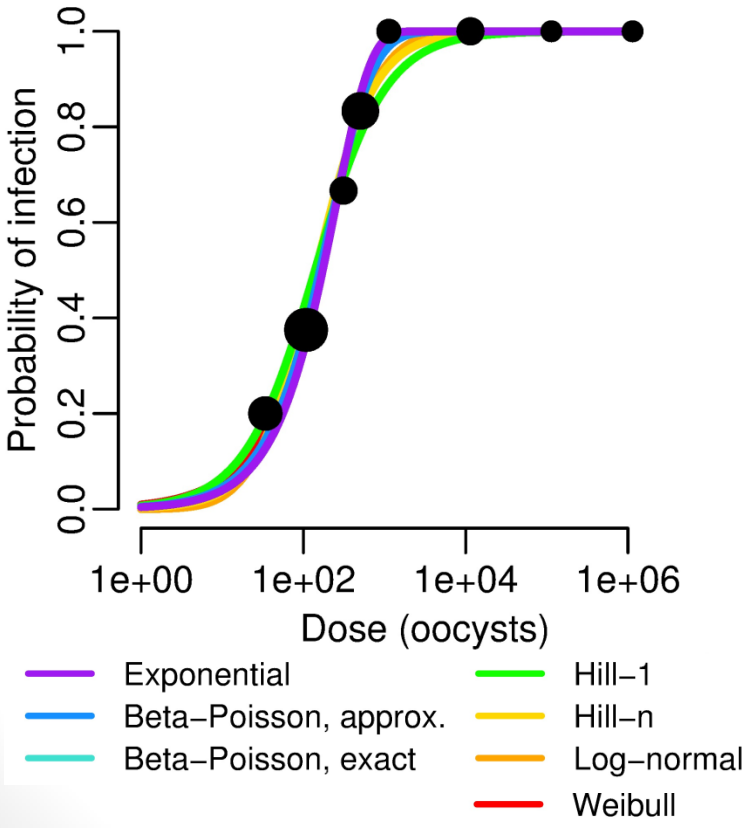
- *Cryptosporidium* is a genus of parasitic protozoa that cause gastrointestinal illness (cryptosporidosis).
- The spore form (oocyst) is environmentally hardy and resists chlorine disinfection.





Example: *Cryptosporidium*

- Dose-response data is available for the Iowa strain of *C. parvum* in Dupont et al. 1995 (NEJM).

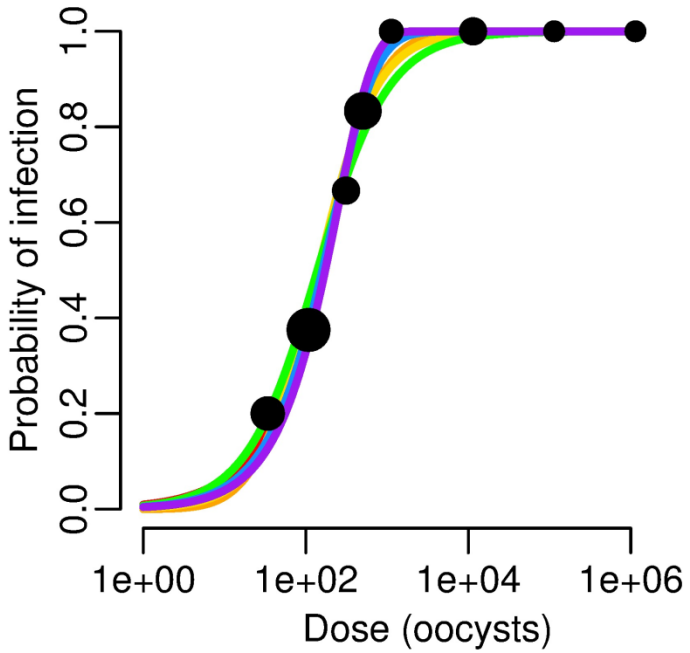


- We fit six dose-response functions to this data.
- We use the functions in an EITS model (with exposed compartment) parameterized to loosely represent *Cryptosporidium*.

Brouwer et al. 2017. Plos Comp Bio.

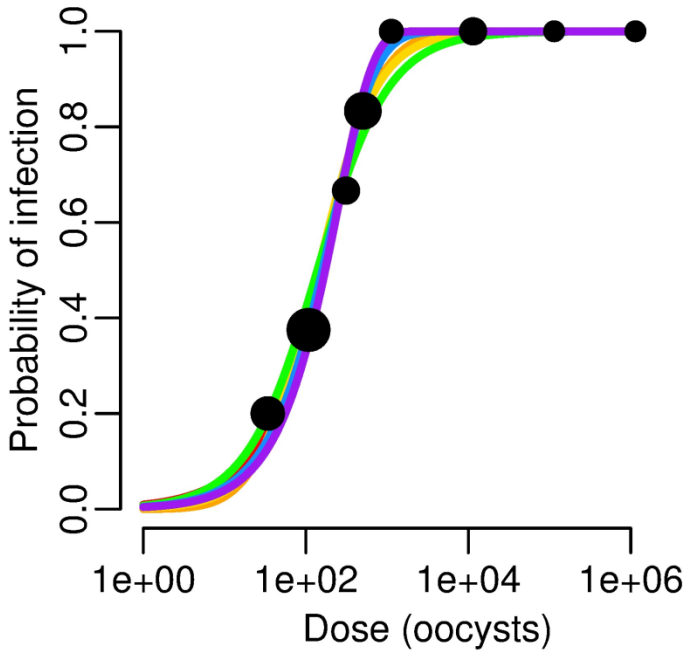
Example: *Cryptosporidium*

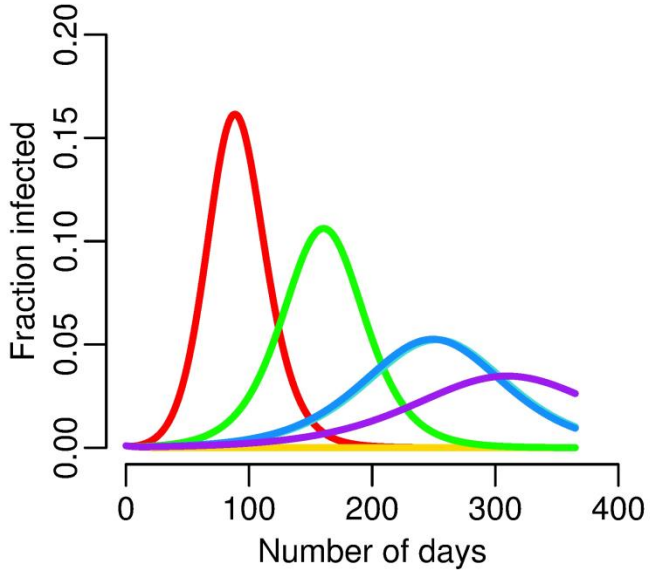
$$\dot{S} = -S \times (contact\ rate) \times f(dose)$$



Example: *Cryptosporidium*

$$\dot{S} = -S \times (contact\ rate) \times f(dose)$$





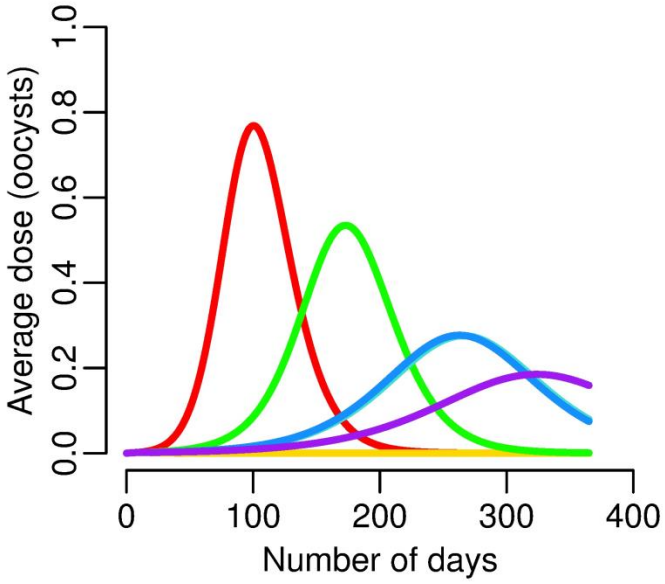
What appears to be good agreement in dose-response functions creates dramatically different dynamics!

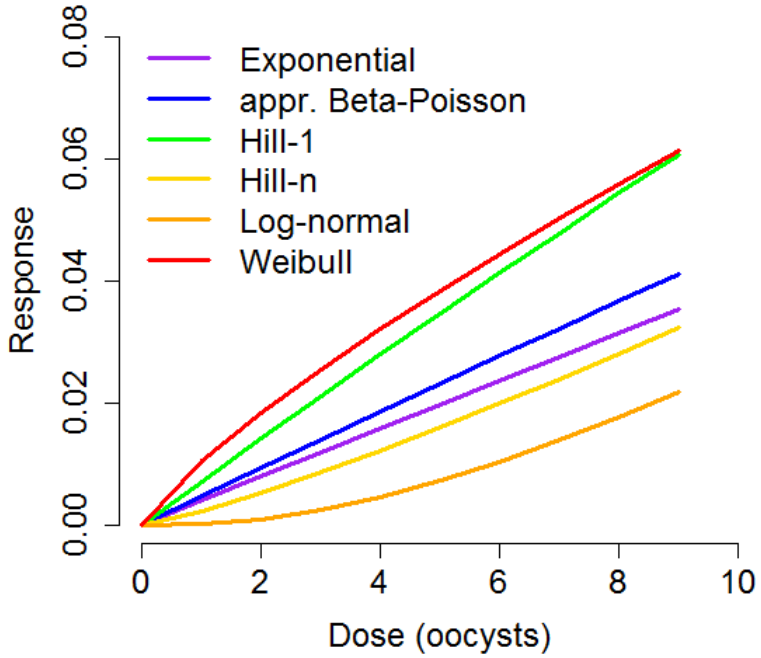
Example: *Cryptosporidium*

- Why are medium and high dose data so uninformative for disease dynamics?

Example: *Cryptosporidium*

- Why are medium and high dose data so uninformative for disease dynamics?
- There is significant spread in the low-dose regime, where the dynamics are actually happening.





This is a problem

- Experimental data is well-fit by many dose–response functions, but these all give very different dynamics.
- Dynamics are controlled by the low-dose regime, but we have little-to-no experimental data there.

Is this modeling approach futile?

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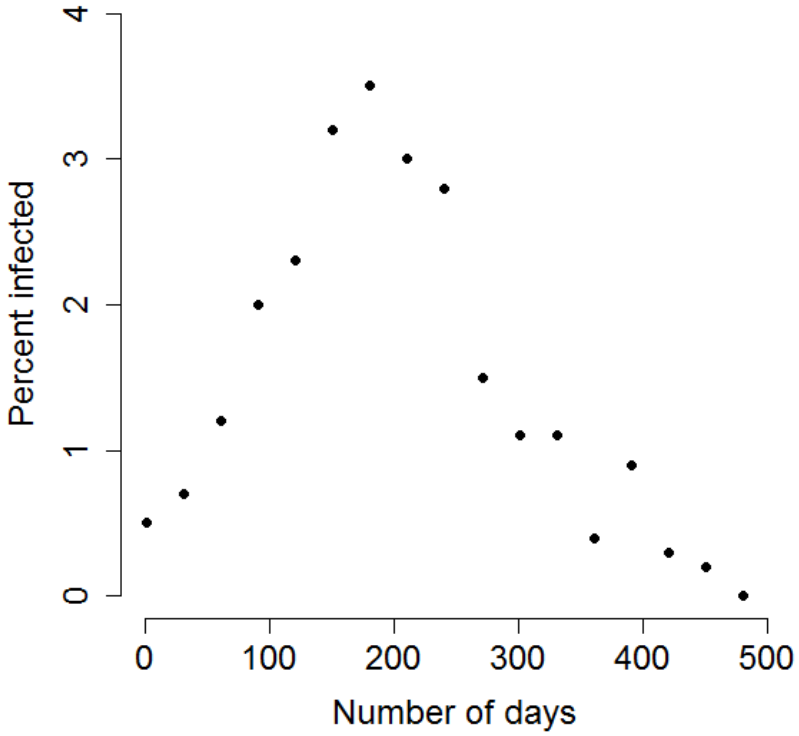
- Not necessarily!

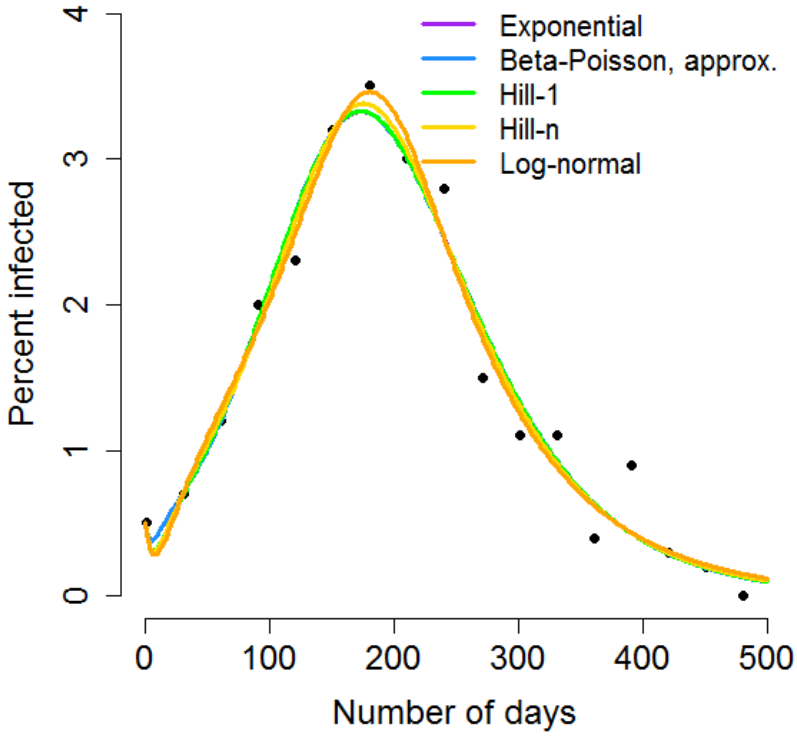
Is this modeling approach futile?

- Not necessarily!
- The previous example assumes that we know all of the other parameters, like shedding and pick-up rate, but this is unrealistic.
- We can manage multiple sources of uncertainty with identifiability analysis, and environmental monitoring can provide additional information.

Fitting to data

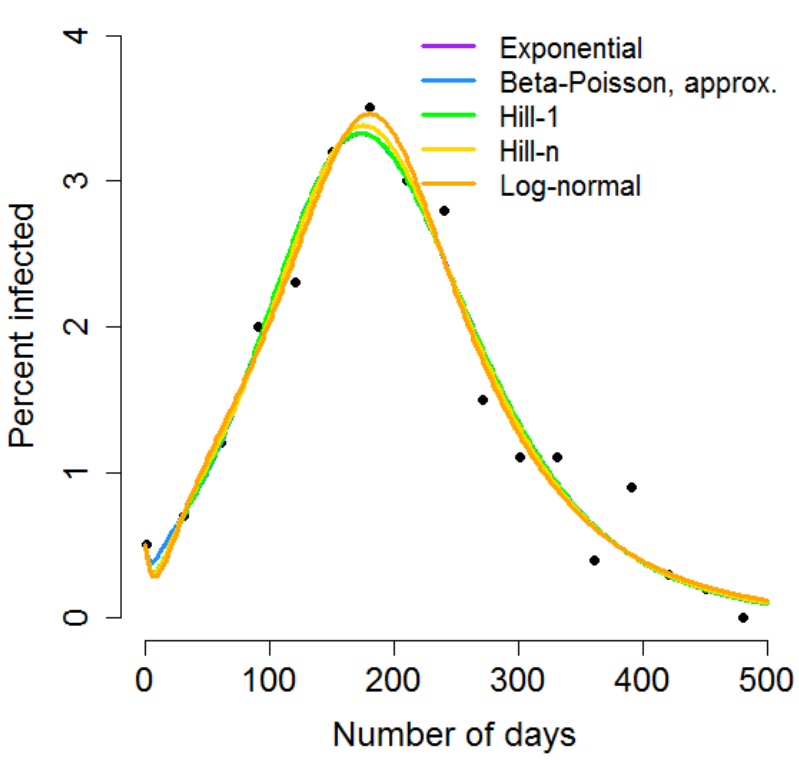


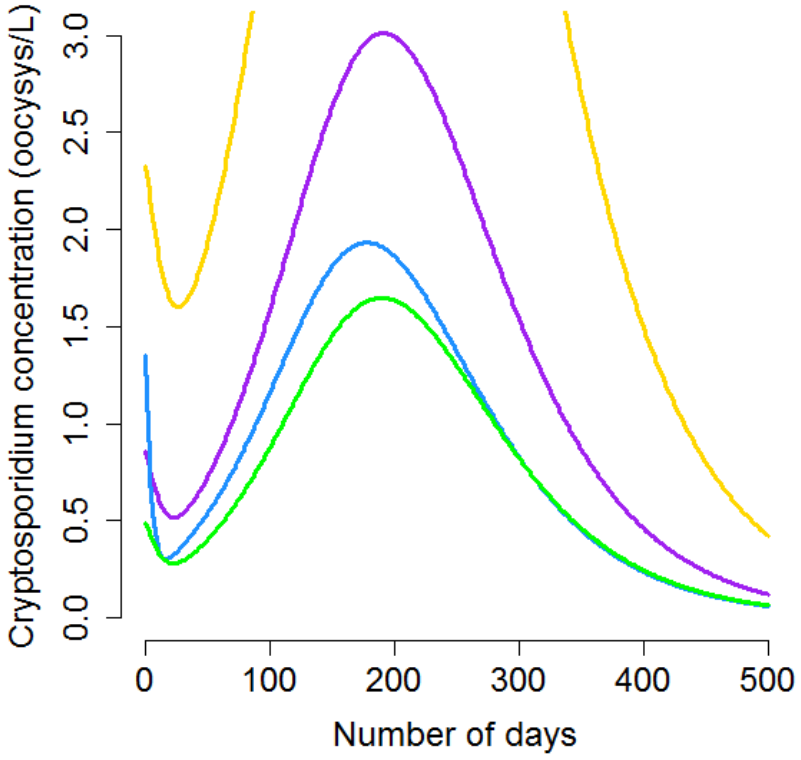
Fitting to data



Different dose response models can fit the data equally well.

Fitting to data





But the different models predict different pathogen concentrations.

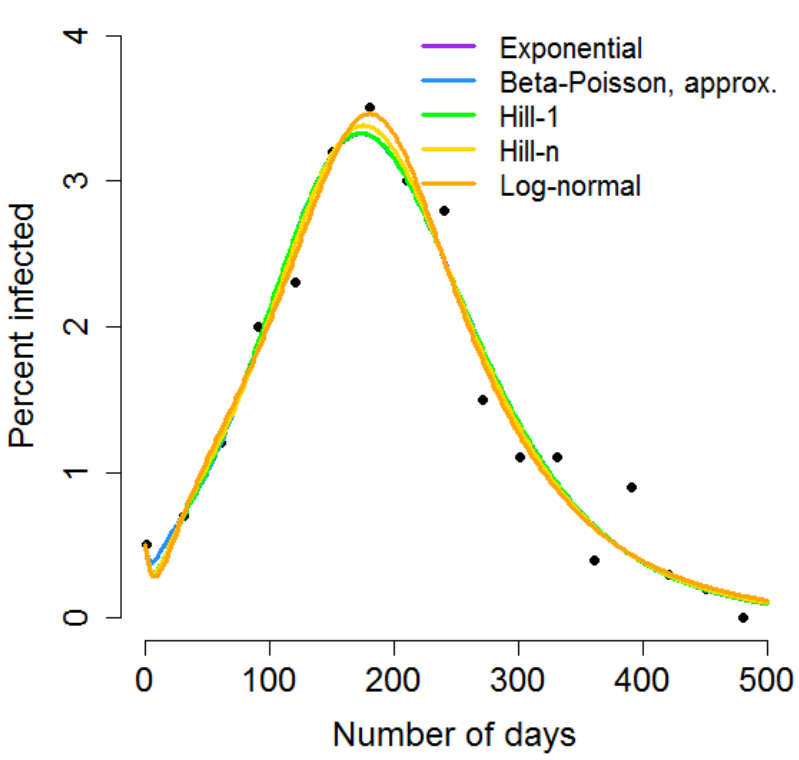
Infectivity and shedding

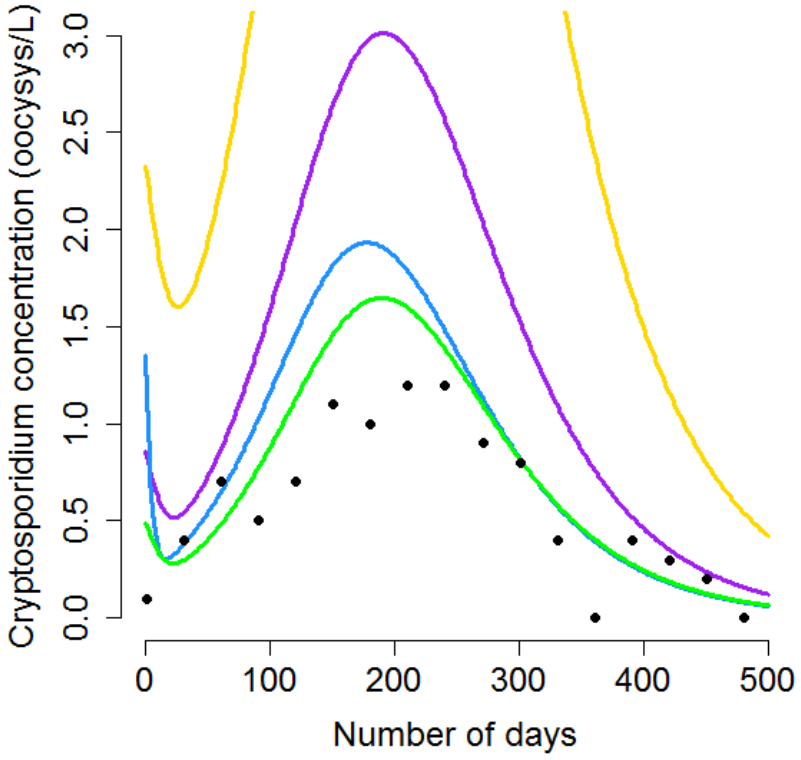
- The low-dose infectivity and the shedding rate can trade-off (i.e. are in the same identifiable combination) to give the same case data.
  - Fewer, highly infectious pathogens
  - More, less infectious pathogens

Infectivity and shedding

- The low-dose infectivity and the shedding rate can trade-off (i.e. are in the same identifiable combination) to give the same case data.
  - Fewer, highly infectious pathogens
  - More, less infectious pathogens
- Observing the concentration of pathogens in the environment could point us to the right place on the continuum.

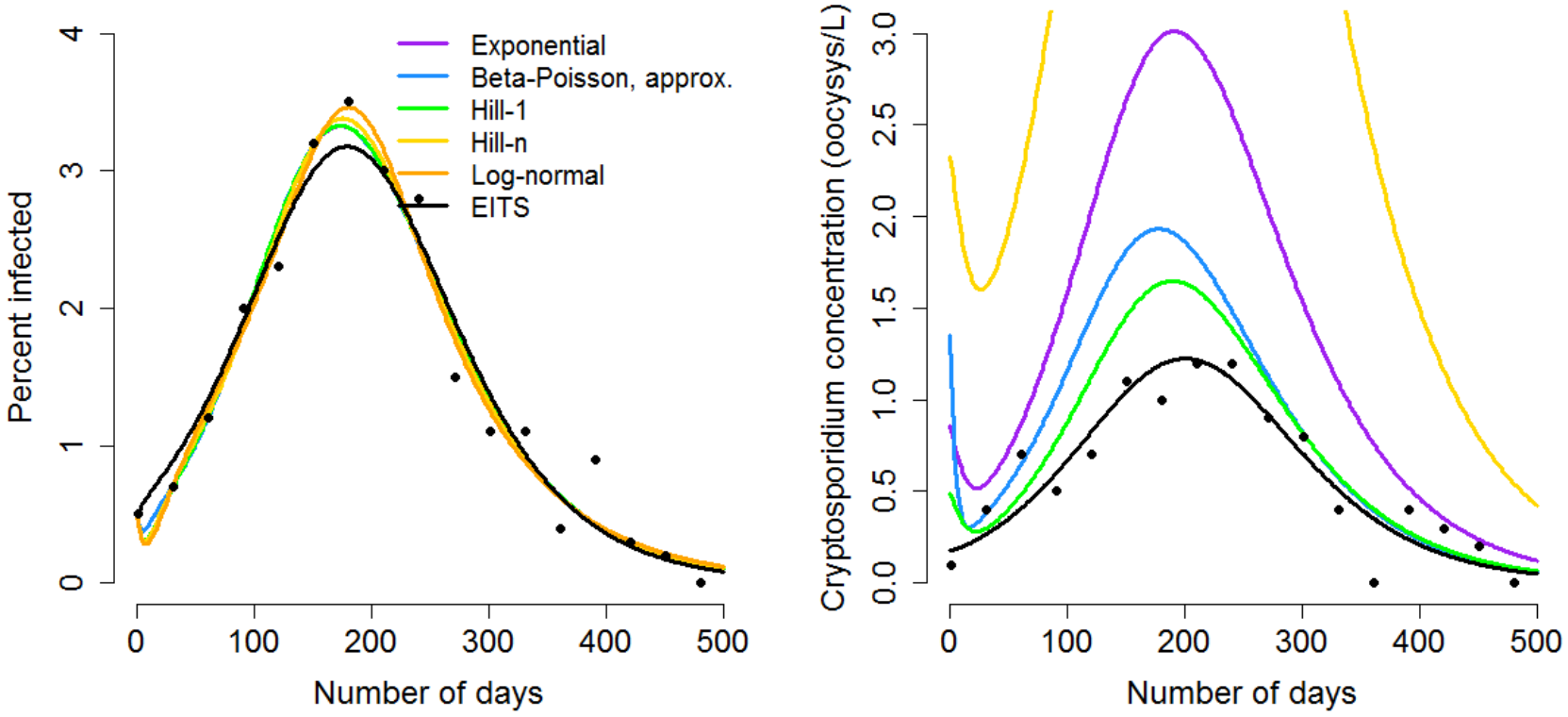
Fitting to data





So, if we measure the environment…

Fitting to data

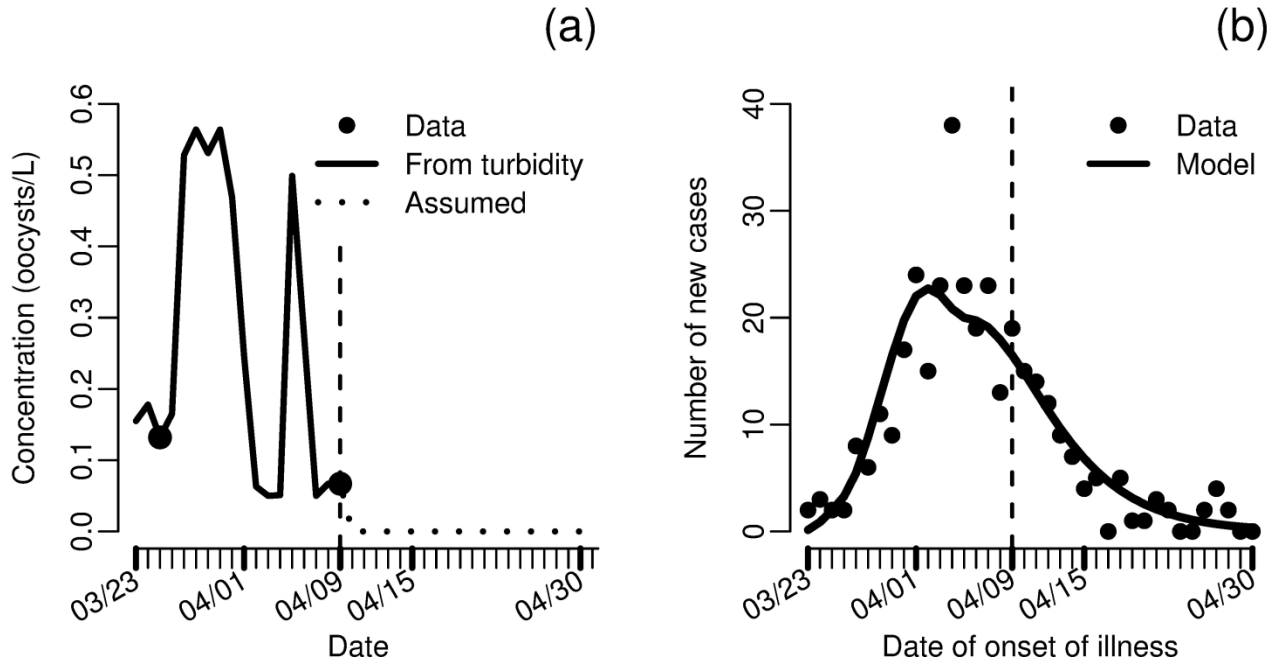


… we can fit to both data sets using a linear model. This approach allows us to estimate, not fix *a priori*, the infectivity.

Milwaukee *Cryptosporidium* outbreak

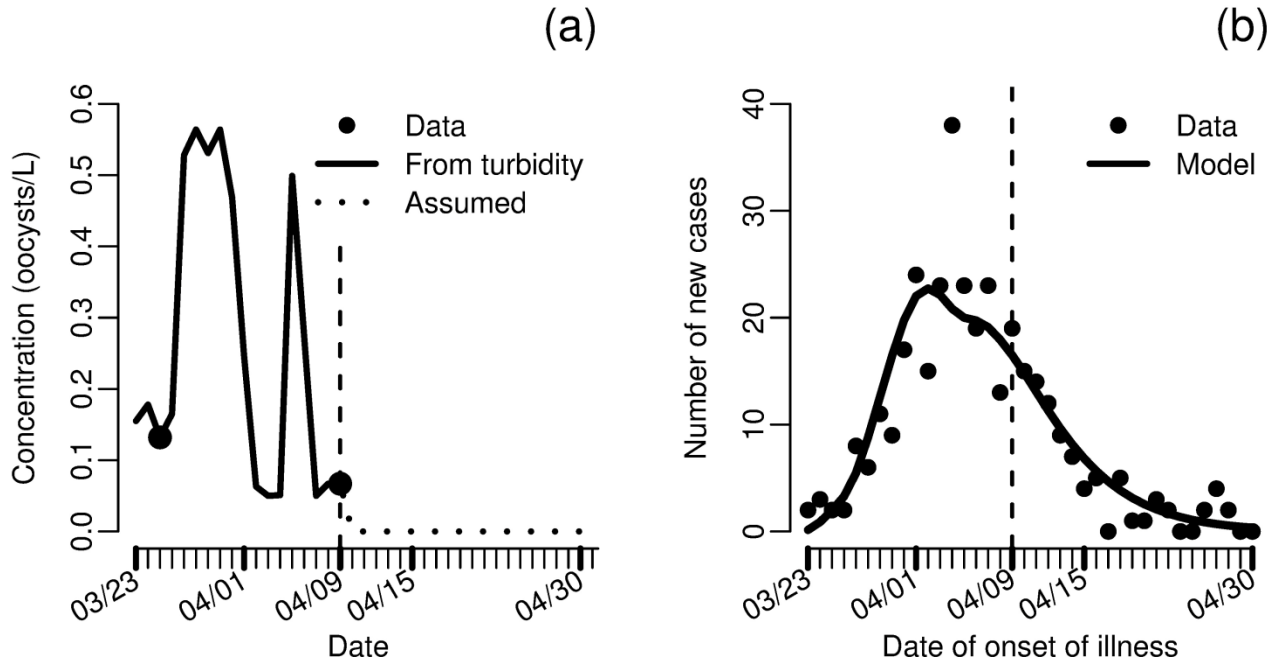
- In March of 1993, one of Milwaukee's two water treatment plants malfunctioned.
- Cases of watery diarrhea began shortly thereafter.
- *Cryptosporidium* was isolate from stool samples.
- Approximately 400,000 people were affected.
- Turbidity was recorded daily, but only two water samples were tested for *Cryptosporidium* concentration.

Milwaukee Outbreak



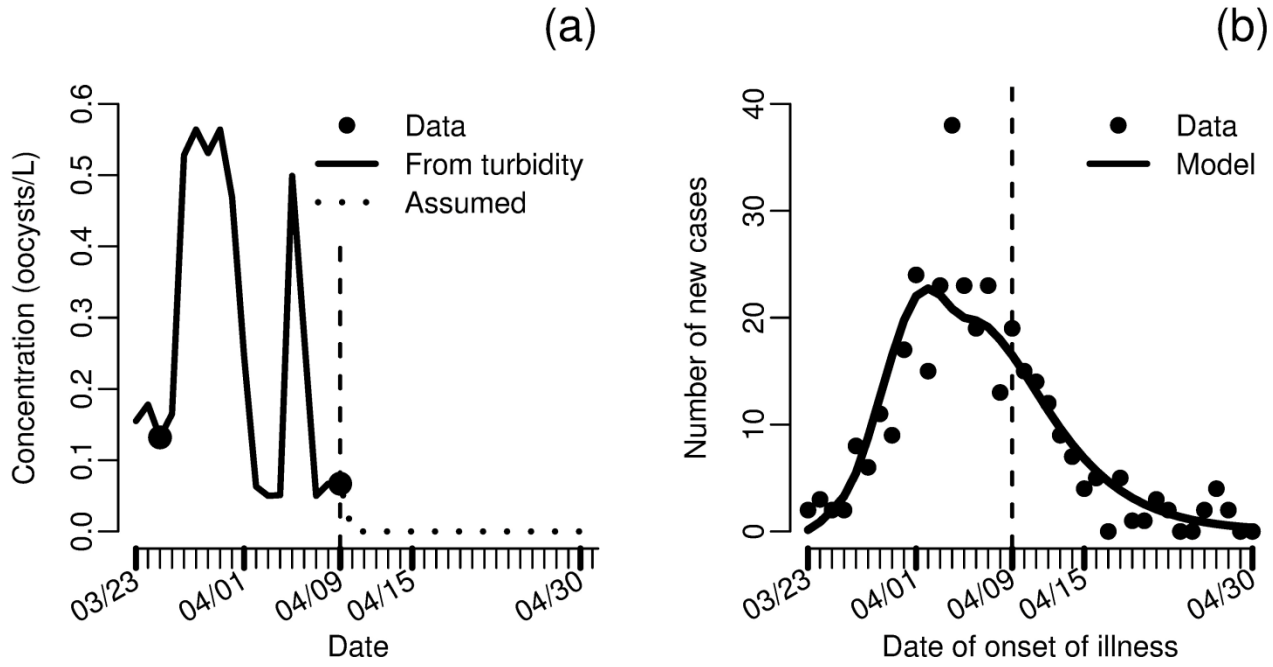
- Here, we use turbidity data as a proxy for exposure to the pathogen compartment, and fit the model to the case data.

Milwaukee Outbreak



- We can estimate, under reasonable assumptions of water consumption rates, that the infectivity was an order of magnitude greater than the Iowa strain of *C. parvum*, much closer to the TAMU strain.

Milwaukee Outbreak



- Environmental monitoring can help us estimate infectivity from data, instead of being forced to assume an infectivity from a dose–response form.

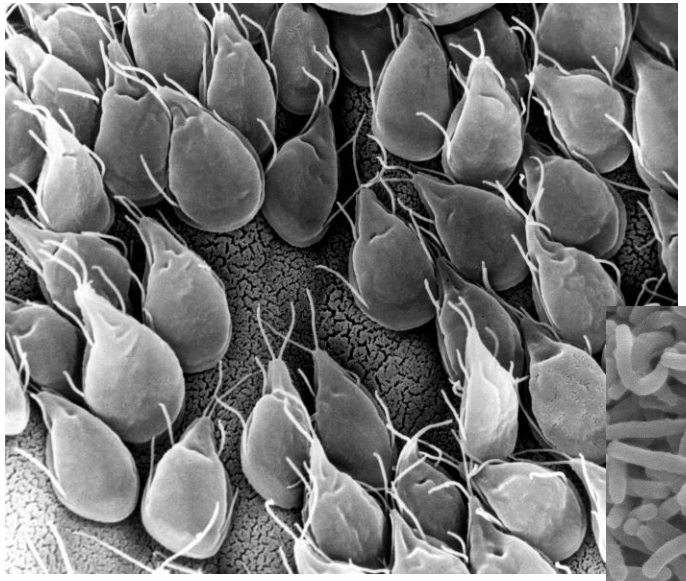
Final thoughts

- Most dose-response data is in the middle and high dose regime, but it is the low dose regime that governs dynamics.
- Constraining functions at higher doses does not satisfactorily constrain behavior at low-doses.
- Statistical “best-fit” is only one of many criteria that should be taken into account. Biological mechanism and realism of the low-dose regime should be primary.

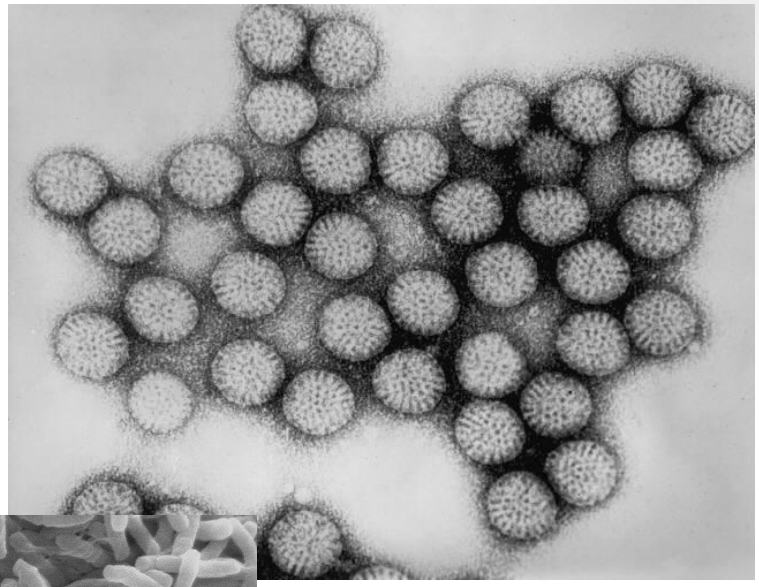
Final thoughts

- Incorporating the environment into models:
  - better understanding of the role and importance of underlying environmental processes.
- Can assess potential interventions:
  - more effective intervention design and allocation of resources.
- Significant challenges remain.
  - Low-dose regime of dose-response functions

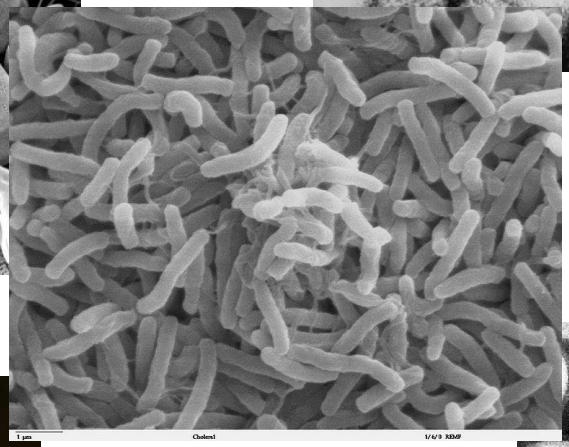
Thank you!



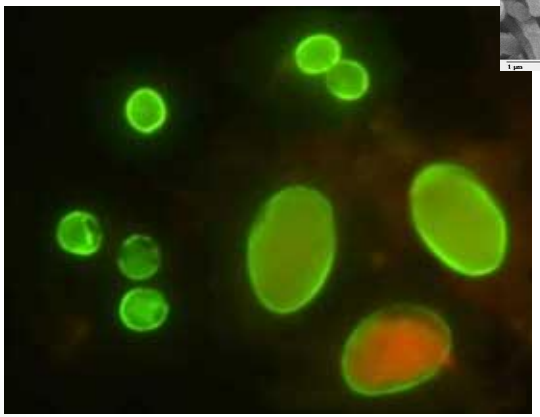
Giardia



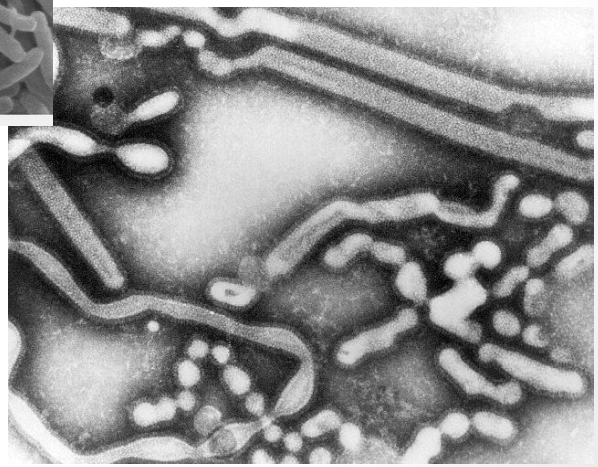
Rotavirus



Cholera



Cryptosporidium



Influenza