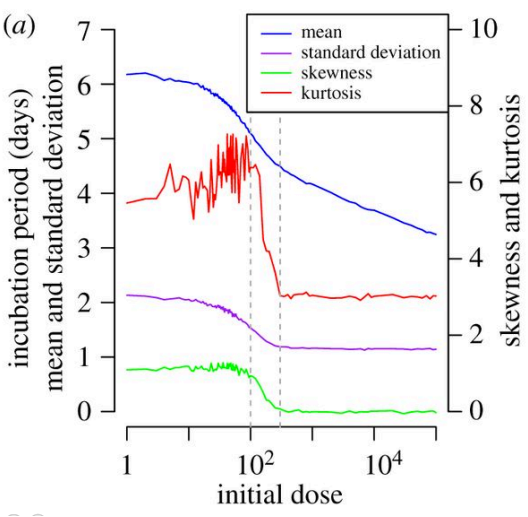
Predicting the Dynamics of Infections with strong Dose-Dependent Responses.

This project naturally follows from the RSG with the same title, and likewise can be expanded in multiple directions.

Background:
Traditional models of infection are overwhelmingly based on a binary state for infection – a host is either infected or it's not (Keeling & Rohani 2008). More recently models have been developed that account for time since infection, allowing insights into time varying infectivity profiles. (For example with HIV, it is now well documented that infectivity is high just after infection, and then reduces until the late stages of infection.) An additional complexity is that individuals are often highly heterogeneous, some will only exhibit mild symptoms and therefore (it is assumed) low levels of onward transmission, while others will have severe symptoms and will likely generate many secondary cases – often referred to as the super spreader effect (Stein 2011). (For example, in the SARS outbreak in Hong Kong single super-spreading events are thought to have infected hundreds of secondary cases.)

This project takes this heterogeneity one stage further by considering the link between infecting dose and the outcome in the individual. It is well known that the strength of the infecting dose has a strong impact on the subsequent infection dynamics: in animal challenge experiments, animals are often inoculated with a dose orders of magnitude higher than natural exposure and its can change the course of infection; for HIV, there have been documented cases of very low-level exposures that have not led to infection. This type of dose response may be responsible for much of the heterogeneity observed between individual infections.

Aim of the project:
This project will build on the close working relationship between PHE and MathSys / WIDER, and will develop a range of models to quantify the impact of dose-dependent dynamics at the individual and population scales. The project can therefore progress in two main (and complementary) directions:



Within-host. PHE has already developed a simple host-pathogen model for *F. Tularensis* (Wood *et al* 2012) and recently extended the model to account for deposition (the short timescale mechanism for clearance of contamination through respiration), which changes the parameters drastically.
No attempt has been made to consider the adaptive immune response at present, nor the impact of medical countermeasures. The timing of medical intervention may be critical to survival of patients. This project would be looking to consider extensions to the current model, incorporating these elements and possibly extending to include migration around the body and so investigate the role of local thresholds for infection (rather than the current whole body model). At present the current literature hasn't been investigated and so a limited scoping study might be of benefit to see alternative modelling approaches in different animals. Other intracellular bacteria also show signs of chronic rather than acute infection

(e.g. Q fever). Is this chance, because of some spatial effect in the body or some "dynamical system" quasi-steady-state behaviour, or some other reason?

Between-hosts. There is obviously an important feed-back between the dose an individual receives and the dose that they can pass on to other individuals. Understanding how this is realised at the population-level is a major challenge. One of the key aspects is breaking away from the standard mean-field (random-mixing) models of infection, and realising that each individual only interacts with a small pool of others (Danon *et al* 2012); this means that rather than a weak inoculum being distributed across the entire population it is most likely aggregated in a few dominant contacts. By modelling contacts and infecting doses as Negative Binomial distributions, it may be possible to make some semi-analytic progress and hence help to generate a novel type of disease model.

As a further extension the modelling approaches at the two scales can be combined.

References.

- Danon, L., House, T.A., Read, J.M. and Keeling, M.J. (2012) Social encounter networks: collective properties and disease transmission. *J. Roy. Soc. Interface* **9** 2826-2833.
  http://rsif.royalsocietypublishing.org/content/9/76/2826

- M.J. Keeling & P. Rohani (2008) *Modeling Infectious Diseases in humans and animals.* Princeton University Press.
  http://press.princeton.edu/titles/8459.html

- R.A. Stein (2011) Super-spreaders in infectious diseases. *Int. J. of Infect. Diseases.* **15** e510-e513
  http://www.sciencedirect.com/science/article/pii/S1201971211000245

- R. M. Wood, J. R. Egan, I. M. Hall (2014) A dose and time response Markov model for the in-host dynamics of infection with intracellular bacteria following inhalation: with application to *Francisella tularensis*. *J. Roy. Soc. Interface.* **11** 20140119.
  http://rsif.royalsocietypublishing.org/content/11/95/20140119