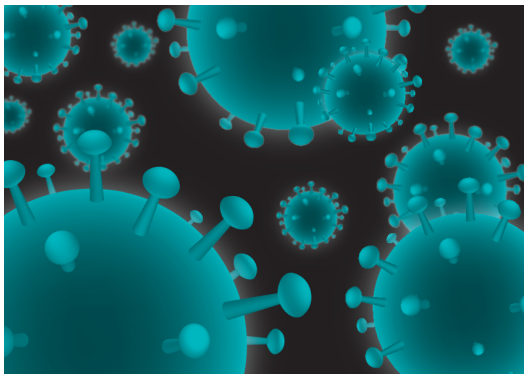
The AMSI workshop on Infectious Disease Modelling Proceedings

Newcastle City Hall
25–27th September 2013



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Programme

Time	**Wednesday**	**Thursday**	**Friday**
08:20-08:45	Registration		
08:45-09:00	Opening		
	Model-based scenarios	*Interface between data and scenario-based modelling*	*Translation to policy*
09:00:10:00	Jane Heffernan	Steven Riley	Matt Keeling
10:05-10:35	Jana Petravic	Nick Beeton	Glenn Fulford
10:35-11:05	Meksianis Ndii	Mykola Pinkevych	Laith Yakob
11:05-11:40	**Morning tea**⋆		
	Model-based scenarios	*Micro-simulation*	*Data analysis /estimation*
11:40-12:10	Mick Roberts	Nicholas Geard	Stephen Petrie
12:10-12:40	James Trauer	Tony Green	James McCaw
12:40-14:00	**Lunch**⋆		
	Data analysis /estimation	*Interface between data and scenario-based modelling*	
14:00-15:00	Alex Cook	Stephen Davis	*Discussion and networking session*
15:00-15:30	Andrew Black	*Poster Presentations*	
15:30-16:00	**Afternoon tea**⋆		
16:00-17:00	*Discussion and networking session*	*Poster Presentations*	*Closing*
18:00-18:30		Pre-dinner drinks (foyer)	
18:30-21:30		Dinner (Hunter room)†	

⋆ Served at the back of the Hunter room.
† Included with conference registration.

Keynote Speakers

Jane Heffernan

Jane Heffernan is an Associate Professor at York University and leads the Modelling Infection and Immunity Lab, which is affiliated with the Centre for Disease Modelling. Heffernan's research projects focus on the development of new biologically-motivated models of infectious diseases, both deterministic and stochastic.

The Effects of Mass Media in Epidemics

Reports on the number of infections and disease in mass media can influence social behaviour during an infectious disease outbreak/epidemic. However, individuals can also become desensitized to this information over time. We have developed a mathematical model which incorporates both mass media induced changes in social behaviour, and desensitization to media reports. Model results show that key epidemic measurements depend on the rates of change in social behaviour and desensitization. Results also show a similar epidemic curve to that observed during the H1N1 pandemic.

Alex Cook

Alex Cook is an Assistant Professor in the Saw Swee Hock School of Public Health, and the Department of Statistics and Applied Probability of the National University of Singapore, as well as in the Program in Health Services and Systems Research at the Duke-NUS Graduate Medical School Singapore. Cook models infectious disease phenomena as stochastic processes and uses inference.

Forecasting public health threats: pandemic influenza, dengue and diabetes in Singapore

The health of populations is threatened by infectious and non-communicable diseases, but when these threats are emerging—either because of a novel pathogen, or a fundamental change in lifestyles—the past is not a reliable guide to the future. Predicting the future of an infectious disease epidemic, or a non-communicable 'epidemic', is a risky but necessary endeavor to guide policy making. In this talk, I will describe a triplet of models/applications that my team and collaborators in Singapore have worked on and which have guided policy making in our Ministry of Health, Ministry of the Environment and Water Resources, and Ministry of Defence. The applications are real-time, on-line forecasting of the 2009 influenza A(H1N1) pandemic, dynamic forecasts of the record-breaking dengue epidemic of 2013, and 35 year projections of the burden of type two diabetes in rapidly aging, increasingly sedentary Singapore. We use a combination of compartmental, statistical and individual-based models.

Steven Riley

Steven Riley is a Reader in Infectious Disease Ecology and Epidemiology in the School of Public Health at Imperial College London. Riley studies the transmission of human pathogens by both collecting data and using mathematical models to look at interesting scientific questions that are relevant to public health.

Disease Dynamics of Respiratory Viruses

The health of individuals is constantly being challenged by well-established respiratory viruses, while national and international health policy-makers must concern themselves with the best way to respond to looming pandemics. Mathematical models, as a key methodology of disease dynamics, are now frequently used to address a wide set of interesting and important questions related to their emergence, eradication, and just about everything in between. In this talk, I will present a simple conceptual model of the full cycle of human-pathogen interaction for respiratory viruses before discussing in more detail a few of the different questions that have concerned me over the years. For each question, I will highlight the key refinements to the simple model that were necessary. I will echo many others and propose that in addition to further technical work on the methodology of infectious disease models, we should also be trying to gather primary data because that might be an easier way of getting a robust answer for some key questions (and no one else is going to go and get the data for us). In the last section of the talk, I will describe initial results from two ongoing disease dynamic field studies of influenza. However, as it turns out, primary data does not free us of the need for better models because even when the data answer the question you were interested in, they always seem to raise several additional interesting questions. I will conclude by suggesting priorities for the future development of mathematical models of viral respiratory pathogens.

Matt Keeling

Matt Keeling is a Professor in both the Mathematics Institute and Department of Biological Sciences at the University of Warwick. Keeling is an internationally-renowned researcher in the mathematical modelling of infectious diseases and co-authored the prominent book Modeling Infectious Diseases: in humans and animals.

Optimal Control

One of the primary uses of mathematical models in epidemiology is to determine effective (and ideally optimal) control strategies. In this talk I'll present recent work in this area and focus on the need for more sophistical methodologies. In the majority of applied situations, researchers rely on repeated simulation of a range of alternative control options from which they can pick the strategy with the 'best' behaviour. However, such an approach is computationally intensive. Instead we look at household models where exact results for optimal prophylactic vaccination are available, and extend these ideas to metapopulation models. Finally we consider the complex problem of reactive vaccination and consider a simple two-patch model where exact results can be obtained.

Posters

A model for the establishment of tick-borne pathogens

Ms Jessica Dunn
Stephen Davis, Andrew Stacey, Maria Diuk-Wasser

The basic reproduction number of a pathogen, R_0, determines whether a pathogen will spread (R_0 greater than one), when introduced into a fully susceptible population or fade out (R_0 less than one), because infected hosts do not, on average, replace themselves. We develop a simple mechanistic model for the basic reproduction number for a group of tick-borne pathogens that wholly, or almost wholly, depend on horizontal transmission to and from vertebrate hosts. This group includes the causative agent of Lyme disease, Borrelia burgdorferi, and the causative agent of human babesiosis, Babesia microti, for which transmission between co-feeding ticks and vertical transmission from adult female ticks are both negligible. We then define parameter ranges for the 19 parameters using estimates from the literature, as well as laboratory and field data, and perform a global sensitivity analysis of the model. This enables us to rank the importance of the parameters in terms of their contribution to the observed variation in R_0. We conclude that the transmission efficiency from the vertebrate host to Ixodes scapularis ticks, the survival rate of Ixodes scapularis from fed larva to feeding nymph, and the fraction of nymphs finding a competent host, are the most influential factors for R_0. This contrasts with other vector borne pathogens where it is usually the abundance of the vector or host, or the vector-to-host ratio, that determine conditions for emergence.

A model for respiratory syncytial virus (RSV) transmission

Miss Alexandra Hogan
Geoff Mercer, Kathryn Glass, Hannah Moore

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory infections in infants and young children. As infection with RSV does not cause long-lasting immunity, individual children may be repeatedly infected. Almost all children are infected by the time they reach two years of age and studies show that the incidence is higher for children aged less than 12 months that for those aged 12-23 months.

In temperate climates, RSV dynamics are highly seasonal, with mid-winter peaks and very low levels of activity during summer months. We present a SEIRS model for RSV transmission, for two age classes, where the transmission rates are seasonally forced. Parameters are estimated from the available literature.

The model shows either a distinct biennial seasonality (such as that seen in Australian climate data), or annual peaks of the same magnitude, depending on parameter values. Future work will involve expanding the model and fitting to a population-linked laboratory data set for the metropolitan region of Western Australia. Further, with a new vaccine for RSV currently being trialled, we will investigate the optimal timing in the transmission cycle for the roll out of a vaccination program.

Modelling transmission and interventions for MRSA and VRE in a hospital setting

Mr Xing Lee
with Glenn R. Fulford, Anthony N. Pettitt

Two common causes of healthcare-associated infections that are of increasing concern are methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) due to difficulty in detection, prevention and treatment of these antibiotic-resistant pathogens. Explorations into the different possible modes of transmission for these pathogens, for example contact with colonised individuals or transmission via environmental contamination, along with effects of intervention strategies have mainly been done through simulation studies using mathematical models due to difficulties in collecting appropriate information from randomised controlled trials or observational studies alone. However, the dominant transmission modes for such pathogens have yet to be clearly ascertained. We provide an overview of mathematical models particular to the spread of these nosocomial pathogens within a hospital setting as well as some preliminary simulation-based investigations which also incorporates effects of various interventions.

Epidemics on Networks

Miss Karen McCulloch

Recently, it has become apparent in the literature that the structure of a contact network can significantly impact the way an infection spreads through a population.The assumption that every individual is connected to every other individual (homogeneous mixing) within a population has been used extensively in models for the spread of infection on networks. This assumption is not adequate for many types of infectious disease as the number of contacts each individual has within the population may vary. The spread of infection on traditional heterogeneous network structures such as scale-free, small-world, lattice and random networks have also been studied both numerically and analytically in the literature. However, there is still a need for more extensive analytical results for heterogeneous networks which differ from these traditional network structures.

The dynamics of an SIR (Susceptible-Infected-Recovered) epidemic process on small networks with different topological structures are investigated in order to better understand how the structure of a contact network impacts the transmission of infection throughout a population.

With a network of N nodes, the state space for an SIR model consists of 3^N possible states. These states may be lumped together based on symmetries of the network. In the most simple case of a complete network, states that have the same number of S, I and R nodes can be lumped together. For networks which are not complete we must look at the topology and the number of nodes in each infection state before determining which system states can be lumped together. Differential equations which describe the transition of the network between the lumped states are derived. The individual final size probabilities are found analytically and a final size distribution produced for each of the small networks. The final size is the total number of individuals that were infected at some point during the epidemic.

Modelling Infectious Disease in a Plant Crop

Miss Carol McInerney

This poster will outline a simulated example of a disease model for an agricultural crop and the methodology used to develop it. Firstly, the disease data will be generated by adding random noise to an SIR type model and comparing it to yield data generated by the Agricultural Production system SIMulator (APSIM). APSIM is the most widely used agricultural modelling tool in Australia and has been shown to accurately predict crop yield for a range of agricultural crops. Having said this, APSIM does not take into consideration any loss due to disease when estimating the yield of a crop for a given season. Disease data will be generated by finding any difference between the yield predicted by APSIM and the observed data. Using this data I aim to assess the fit of a variation of the SIR model. Primarily, I will explore an SIRX model, which includes compartments for two different sources of infection. This is useful for soil-borne pathogens, where primary infection from free-living inoculum occurs at a different rate to that of secondary infection, namely from plant to plant.

Neighborly or Neglect: Sharing a Cup of Malaria

Dr Shawn Means
A. Prof. Robert Smith?

Eradication of malaria from the world in the latter part of the twentieth century proved an elusive albeit desirable objective. Resurgence of malarial incidence is currently underway, and indoor residual spraying - spraying insecticide inside houses to kill the malarial vector mosquitoes - is one of the most effective methods for controlling the spread of this profoundly destructive and deadly disease. However, selective application of spraying excluding communities or dwellings over inconsistent time intervals may be self-defeating, permitting a foothold for subsequent vector invasion. We extend prior work modeling the effects of temporally inhomogeneous spraying programmes and some spatial distribution into a fully spatio-temporal model. Our aim is determining the effects of the following on potential resurgence of malaria due to 1) inconsistent spatial distributions and temporal sequences of spraying; 2) spatial density of communities and 3) terrain effects such as proximity of undeveloped land or bodies of water. We consider initially communal density effects in our preliminary investigation.

Cross-border tuberculosis transmission in the Torres Strait Island–PNG region

Dr Roslyn Hickson
G.N. Mercer, E.G. Thomas, K.M. Lokuge

Tuberculosis (TB) is a growing problem worldwide, especially with the emergence and high prevalence of multidrug-resistant strains. We develop a metapopulation model for TB spread, which is particularly suited to investigating transmission between areas of high and low prevalence. A case study of cross-border transmission in the Torres Strait region of Australia and Papua New Guinea (PNG) is considered and a sensitivity analysis is conducted. We find that only 6 of the 50 parameters analysed are important to the cumulative number of clinically active TB patients in the entire region. Of these, only the detection rate in PNG is found to be an important intervention parameter. We therefore give insight into the extent the area with the high burden of TB (PNG in the case study) is dominating the TB dynamics of the entire region. Furthermore, the sensitivity analysis results give insight into the data that most important to collect and refine, which is found to be data relating to the PNG parameters.

Contributed Talks

Devil in the details – mechanistic modelling for conservation and public health

Dr Nick Beeton
Hamish McCallum, Grant Williamson, Joanne Potts, Scott Carver, Larry Forbes, Chris Johnson
Topic: *Interface between data and scenario-based modelling*

There is a large and increasing scope for modelling to help inform management policy for infectious diseases. However, to do so effectively requires a rigorous approach to developing models based on both field data and the best available knowledge of the species' biology. With this aim in mind, we present a series of mechanistic mathematical models describing the transmission process of two infectious diseases: Devil Facial Tumour Disease (DFTD), an infectious cancer currently threatening the Tasmanian devil; and Ross River fever, a human disease caused by the vector-borne Ross River virus (RRV). The presented models cover compartmental Ordinary Differential Equation models (ODEs) and spatially explicit population models using reaction-diffusion equations, using various sources of data to construct, parameterise and test the models. Some example projections will then be presented, and their implications for the study species examined.

Parametrising Markovian epidemic models using household level data

Dr Andrew Black
J. V. Ross.
Topic: *Data analysis/estimation*

It has become common that during the outbreak of a new disease data is collected at the household level to try and understand the dynamics of the disease. Typically cohorts of households are monitored and onset times for various symptoms are recorded. This leads to statistics such as the serial interval, which is the time from the onset of symptoms in a primary case and the date of symptom onset in one of its secondary cases. I will discuss some work Joshua Ross and myself have done on using this type of household level data for parameter inference using Markovian models. The overall goal here is to use data collected at the household level during the early stages of an outbreak to parametrise population level models and hence inform public health policy.

Babesiosis Emergence in the United States

Dr Stephen Davis
Jessica Dunn, Maria Diuk-Wasser
Topic: *Interface between data and scenario-based modelling*

Human babesiosis is an emerging tick-borne disease in the United States caused by the protozoan parasite Babesia microti. It is transmitted by the same tick vector (Ixodes scapularis) and shares the same main reservoir (white-footed mouse, Peromyscus leucopus) as Borrelia burgdorferi, the causative agent of Lyme disease. The geographic range of babesiosis has expanded from coastal islands, in a similar pattern to the expansion of Lyme disease, but, for reasons not well understood, far more slowly. We present multi-host, multi-pathogen mechanistic models of emergence – R_0 models – and our progress towards validating such models using the present geographical range of babesiosis. Of considerable public health concern is the future geographical range of babesiosis and other pathogens transmitted by I. scapularis. A complicating factor is likely to be climate change because successful transmission of the pathogen is linked to overlap between the host-seeking activities of the larval and nymphal life stages of the tick vector, and these in turn are affected by spring temperatures. Climate change has already been argued to be responsible for the northward expansion of I. scapularis into Canada with Lyme disease rapidly having followed. Our aim is to provide mechanistic models that are as simple as possible and that can be readily parameterised and validated with field data, as a strong scientific basis for scenario-based modelling of babesiosis emergence that might inform public health policy.

MRSA in the community

Dr Glenn Fulford
Kate Halton, Nicholas Graves
Topic: *Translation to policy*

Antibiotic resistant pathogens have become a serious problem in hospitals around the world. The most common is Staphylococcus aureus where the common antibiotic resistant strains are known as Methicillin Resistant Staphylococcus aureus (MRSA). The prevalence of hospital associated strains of MRSA appears to have reduced in recent years,probably due to interventions such as improved hand hygiene, cohorting and the use of decolonisation treatments. However, there is increasing concern about newer strains of MRSA which are circulating in the community since these seem to be replacing the hospital associated strains in hospitals. These newer strains can be more virulent than the hospital associated strains. To minimise the invasion of community associated strains of MRSA into the hospital sector one possible intervention is to restrict elective surgery to those who are known to be uncolonised with MRSA. However, this might involve significant screening and decolonisation costs.

To assess cost effectiveness of different interventions economic modelling combined with transmission modelling appears to be a promising, but under-utilised tool. We describe the development of a stochastic model with compartments for various hospital and community sectors. A key question is to determine what level of detail is needed in the model to be able to provide the right information to answer the appropriate economic questions for this intervention. For example, including a compartments for ICU patients is needed since these patients incur a significant cost. The current model demonstrates the sensitivity to current prevalence levels in the community. Also important to estimate accurately are community transmission rates. High values of community transmission will result in increasing prevalence in the hospital sector. The model is still being developed. The model generally predicts that a policy of ensuring elective admissions are decolonised can reduce the prevalence in the hospital. However further validation of the model is needed before translating model outcomes into policy.

A microsimulation model of pandemic influenza surveillance strategies

Dr Nicholas Geard
Andrew Black, Joshua Ross, James McCaw, Jodie McVernon
Topic: *Micro-simulation*

The collection of enhanced epidemiological data in the early stages of a pandemic influenza outbreak is expected to help estimation of its likely impact, and inform decision-making about the appropriate scale of response. The key characteristic of interest is the effective reproduction number R_{eff} (or number of secondary cases per case), which provides information on how rapidly a pathogen spreads through a population. Enhanced surveillance can expedite estimation of R_{eff} by increasing case detection. Strategies for enhanced surveillance include monitoring household members and non-household contacts of detected cases for illness. This approach was used in the UK during the 2009 H1N1 influenza pandemic to collect enhanced data on the first few hundred (FF100) confirmed cases, and the development of comparable approaches is currently being considered in Australia. Key challenges for the design of feasible and sustainable approaches to enhanced surveillance include balancing the information requirements of estimation algorithms against the costs of surveillance, and accounting for estimation biases that arise from the fact that only a subset of contacts and cases will be detected.

We have developed a computational microsimulation model to simulate both disease outbreaks and surveillance strategies and, by providing synthetic data sets to assist with the development of estimation algorithms, help quantify the information gains associated with extra-household contact tracing. The microsimulation model captures the the demographic, household and contact structure of the population in a detailed and realistic fashion. The disease model provides a complete picture of all cases occurring in the simulated outbreak, while the surveillance model provides the subset of cases that we anticipate will be detected using that particular strategy, and hence are available for the purposes of parameter estimation. Different outbreak scenarios and surveillance strategies can be simulated by varying disease and contact tracing parameters, such as the number of contacts monitored, the duration for which they are monitored, and the timing of cessation.

Initial simulations reveal the extent to which the effectiveness of any given surveillance strategy will depend on the transmissibility and severity of the disease. For example, even when transmissibility is low, if a disease is relatively mild (and visibility is consequently low) the outbreak may have been underway for some time before the first case is detected. The subsequent rapid growth in cases has the potential to exhaust data collection capacity almost as rapidly as would be expected in a more transmissible and severe (and hence more visible) scenario. Estimation algorithms, originally developed for the analysis of empirical surveillance data, have been applied to the synthetic data-sets produced by the microsimulation model and demonstrate good capability to recover disease parameters from the complete data set. These algorithms are currently being extended to account for the partial capture of cases in the detected data set.

Our microsimulation model captures the heterogeneous contact structure and complex patterns of individual-level exposure and transmission that characterise real populations. It therefore provides a useful framework to assist with the integrated development and evaluation of both the surveillance strategies that will be used to collect disease data and the estimation algorithms that will transform this data into actionable knowledge.

A General Microsimulation Framework for Infection Modelling

Dr Tony Green
I. Piper, D. Keep
Topic: *Micro-simulation*

Over the last decade there has been growth in the use of micro-simulation for infectious diseases epidemiology. This differs from macro models in three main respects: all infection processes occur into the individual rather than a cohort of like individuals; the contact time is not coupled to the infection chance; and the infection chance is dependent on the individual infection characteristics of the infectious person and the targeted susceptible individuals.

We have developed a general micro-simulation framework that includes a multiple infection model as well as other modules such as motivation. The ability to specify the immunological characteristics of individuals has the potential to bring together epidemiology, virology and immunology. In this paper, we would like to discuss how this could be achieved with examples from current research.

The influence of changing host immunity on 1918-19 influenza pandemic dynamics

Dr James McCaw
Bolton KJ, McVernon J, Mathews JD
Topic: *Data analysis/estimation*

The sociological and immunological factors which gave rise to the three pandemic waves of Spanish influenza in England during 1918-19 are still poorly understood. Here we explore the role that changes in host immunity, driven by a combination of within-host factors and viral evolution, may play in explaining weekly mortality data and wave-by-wave symptomatic attack-rates available for a subset of English cities. Our results indicate that changes in the phenotype of the pandemic virus are likely required to explain the closely spaced waves of infection, but distinguishing between the detailed contributions of viral evolution and changing adaptive immune responses to transmission rates is difficult given the dearth of sero-epidemiological and virological data available for more contemporary pandemics. We find that a dynamical model in which pre-pandemic protection in older "influenza-experienced" cohorts is lost rapidly prior to the second wave provides the best fit to the mortality and symptom reporting data. Best fitting parameter estimates for such a model are consistent with existing modelling work indicating that post-infection protection lasted of order months, and statistical analyses indicating that population-age was inversely correlated with overall mortality during the herald wave. Our results suggest that severe secondary waves of pandemic influenza may be triggered by viral escape of prior immunity, and thus that understanding the role of heterosubtypic or cross-protective immune responses to pandemic influenza may be key to controlling the severity of future influenza pandemics.

An analysis of a seasonal dengue model with the presence of Wolbachia

Mr Meksianis Zadrak Ndii
Roslyn Hickson, David Allingham, Geoff Mercer, Irene Hudson
Topic: *Model-based scenarios*

An innovative new strategy to combat dengue is currently being trialled in Far North Queensland. This Wolbachia intervention can reduce the level of dengue virus in mosquitoes, and hence reduce their ability to transmit it. We develop a mathematical model for dengue that includes a seasonal term for the mosquito population. This model is used to determine under which Wolbachia-infected mosquitoes can persist in the wild. We determine that Wolbachia can reduce dengue transmission by higher than 90%, and this is influenced by the lifespan of Wolbachia-infected mosquitoes and the reproductive rate. This reduction is not affected by the initial number of imported cases. However, the timing of the introduction of imported cases is very important especially when the mosquito population is at its lowest. The transmission probability, biting rate, and the baseline mosquito death rate are the most are the most important parameters for determining the number of human infected with dengue during a single outbreak.

Impact of the timing of anti-latency drug administration on the outcome of antiretroviral HIV treatment

Dr Janka Petravic
A. Martyushev, J. Reece, S. Kent, M. Davenport
Topic: *Model-based scenarios*

Latently infected cells are considered a major barrier to eradication of HIV. During standard antiretroviral treatment (ART), latently infected cells persist and cause the rebound of virus if treatment is ceased. Several classes of anti-latency drugs currently under investigation show promise as "activating agents" that could reduce the reservoir of latently infected cells. Because of possible toxicity of such drugs, they are usually administered only for a short period of time, and the current strategy is to give them when virus becomes close to undetectable.

Our recent studies have shown that the turnover of the cells latently infected with HIV may be increased in high viral load setting. Taking this result into account, we use mathematical modelling to study the impact of timing of the activating drugs relative to the start of ART on the remaining latently infected cell pool. We find that, depending on the effect of the anti-latency drug on the activation rate of latently infected cells, the optimal timing may be at the very start of ART, and giving them later may severely reduce their efficacy. In order to plan ART in combination with activating drugs, we need better knowledge of their exact mode of action.

Disentangling within-host and transmission fitness in competitive-mixtures experiments

Mr Stephen Petrie
Jodie McVernon, James McCaw
Topic: *Data analysis/estimation*

When investigating the likelihood that an emergent (e.g. drug-resistant) pathogen will spread widely, it is important that we understand how fit that pathogen is relative to other competing pathogens. Relative pathogen fitness involves two different components: within-host replication fitness and host-to-host transmission fitness. Here we outline a method that allows each component to be estimated simultaneously, by fitting an appropriate model to experimental data involving co-infection of competing pathogens in vivo.

Competitive-mixtures experiments involve the co-inoculation of various mixtures of two different pathogens into animal hosts. The relative growth of each pathogen is measured over time, both within each host and across multiple host-to-host transmission events. In principle this experimental technique can be used to probe both the relative replication and relative transmission fitness of one pathogen compared to another.

We have previously analysed these experiments using: (1) a within-host modelling analysis that provides estimates of relative replication fitness; and (2) a technique that provides estimates of relative transmission fitness by comparing the proportion of each pathogen upon transmission from a given infector host, to the subsequent proportion in the corresponding infectee host 24 hours later. Because of the 24 hour gap between each proportion measurement, fitness estimates obtained using this second method conflate transmission and replication fitness to some degree (since, in addition to the proportion changing upon transmission, the proportion also changes over time within the infectee due to differing growth rates between pathogens). Also, the within-host model mentioned in the first method is only appropriate for fitting data from hosts that have been infected via inoculation rather than via natural host-to-host transmission, as greater uncertainty in initial conditions within naturally-infected hosts necessitates that the model have an unworkably large number of fitted parameters.

Here we extend the aforementioned within-host model to include transmission between hosts. This new model allows data from all hosts (both inoculated and naturally-infected) within a given experiment to be fitted simultaneously, reducing uncertainty in parameter estimates relative to those obtained from the within-host-only model. The new model also enables simultaneous estimation of both replication and transmission fitness. Unlike the method that we have previously used to estimate relative transmission fitness, these transmission fitness estimates are not conflated with replication fitness. Lastly, the new model has an improved ability to reject certain hypotheses regarding the underlying biological cause of dynamical differences between each co-infecting pathogen (compared with the within-host-only model).

Our analysis allows simultaneous quantification of the relative replication and transmission fitness of different pathogens in competitive-mixtures experiments, and also reduces uncertainty in within-host parameter estimates compared with the within-host-only model. Inferences made using our new model have the potential to inform scenario-based modelling of the spread of emergent pathogens.

Modelling the mechanisms of naturally acquired immunity to malaria

Mr Mykola Pinkevych
M.P. Davenport, J. Petravic, K. Chelimo, J. W. Kazura, A.M. Moormann
Topic: *Interface between data and scenario-based modelling*

Infection with Plasmodium falciparum can cause severe malaria in adults and children if they lack malaria-specific immunity. In residents of malaria endemic areas, naturally acquired immunity is first characterized by resistance to the clinical manifestations of malaria and eventually resistance to infection. Anti-malarial immunity may act at different stages of the parasite life cycle; liver-stage immunity would block the initiation of new infections and blood-stage immunity could block erythrocyte invasion and/or destroy infected RBC reducing Parasite Multiplication Rate i.e. the number on newly infected RBC (in which parasites survived until the next reinfection cycle) per one previously infected RBC.

In order to understand the impact of stage-specific immunity, we analyzed a treatment-time-to-reinfection study from Western Kenya, where 197 adults and children were treated with artemether/lumefantrin to clear blood-stage parasites. Individuals who had no detectable blood-stage parasites 2 weeks post-treatment were deemed cured and thus any parasitemia during the subsequent 10 week follow-up was considered a new infection. Children were further categorized into three age groups (0-4 yr, 5-9 yr and 10-14 yr). As previously observed, there was a progressive delay in mean time to reinfection associated with age and adults had lower parasite densities and fewer observed 'peaks' of parasites once infected compared to children. The more sensitive PCR assay detects parasites earlier than microscopy, and demonstrates a higher overall prevalence of infection than microscopy alone.

To understand what forms of immunity could reproduce the observed reinfection curves for each age group we used a modeling approach. We first derived the reinfection functions assuming liver-stage (infection blocking) immunity only or blood-stage (growth slowing) immunity only and fitted them to experimental reinfection proportions. We find that both the delay between PCR and microscopy infection as well as the differing reinfection dynamics in different age groups are best explained by a slowing of parasite growth with age. We found that the reinfection curves (both PCR and nicroscopy) could be reproduced by the model with blood-stage immunity where each age group had a distribution in the parasite multiplication rate, with a decrease in the mean of this distribution with age.

To gain further insight into acquisition of immunity we developed a stochastic model of malaria infection and blood stage immunity, incorporating both a strain specific as well as a cross reactive or 'general' immunity to all strains. It was able to capture the observed reinfection rates, and remarkably also the observed levels of parasitemia. The model suggests the importance of rapidly-induced, strain-specific immunity in clearing individual infections, and slowly acquired general immunity in bringing down the average Parasite Multiplication Rate with age and magnitude of peaks of parasitemia.

Understanding the dynamics of naturally acquired immunity provides insights for malaria vaccine development as well as a tool for immuno-surveillance in areas experiencing changes in malaria epidemiology due to malaria control interventions.

Epidemic models with uncertainty: application to influenza

Prof. Mick Roberts
Topic: *Model-based scenarios*

One of the first quantities to be estimated at the start of an epidemic is the effective reproduction number, $\mathcal{R}$. Any forward projection of the epidemic is sensitive to the value of $\mathcal{R}$, but the estimate is subject to error. We replace the value of $\mathcal{R}$ with its estimated probability distribution, and model the forward time-course of an epidemic as a probability distribution of infection incidence, changing over time. We demonstrate the method by analysing the *SIR* model with $\mathcal{R}_0$ specified by a probability distribution instead of a single value. We derive probability distributions for the prevalence and incidence of infection during the initial exponential phase, the peaks in prevalence and incidence and their timing, and the final size of the epidemic. Then, by expanding the state variables in orthogonal polynomials in uncertainty space, we construct a set of equations for the distribution of the solution throughout the time-course of the epidemic. The resulting dynamical system is automatically generated by recurrence relations, and need only be solved once. We apply the method to data from the New Zealand epidemic of *H1N1* influenza in 2009, for which $\mathcal{R}$ was estimated to be 1.25 with confidence limits $(1.07, 1.47)$ at the start of the epidemic. We apply the polynomial expansion method, distinguishing imported cases and local transmission, to simulate a forecasting system that could be used in real time. The results demonstrate the level of uncertainty when making projections based on a limited amount of data. The method can also be used to explore the interaction between two subtypes of influenza A, demonstrating how cross-immunity modulates the differences in epidemiological properties of the variants to determine their within-season dynamics.

Scenario analysis for programmatic TB control in Western Province, PNG

Dr James Trauer
Emma McBryde, Justin Denholm, Saba Waseem
Topic: *Model-based scenarios*

Western Province, Papua New Guinea (PNG) is a challenging region for health care delivery with a major burden of tuberculosis (TB) and close geographical proximity to Australia. We were commissioned by the Government of PNG to perform modelling for programmatic TB control in this province and examined five scenarios representing a range of responses to this problem. We used a ten compartment, deterministic model to represent disease states, incorporating multi-drug resistance, mixing between populations and comorbidities (HIV and diabetes), and subsequently performed an economic analysis based on this modelling. We found that only responses including province-wide scale-up of programmatic management of drug-resistant TB are likely to achieve effective control, with relatively little attenuation of the efficacy of such programs resulting from either cross-border mixing or unrecognised high comorbidity rates. Without such programs, the burden of drug-resistant TB is likely to increase rapidly, becoming the predominant strain and resulting in greater costs in the future. Hospitalisation costs predominate in the economic analysis, with the duration of hospitalisation during the intensive phase of treatment for drug-resistant TB being the greatest determinant of costs.

Correlating Clostridium difficile Control Implementation With Infectious Disease Transmission Model Design

Dr Laith Yakob
Thomas V Riley, David L Paterson, Archie CA Clements
Topic: *Translation to policy*

Clostridium difficile is the number 1 cause of infectious diarrhoea in healthcare settings worldwide. There is an interesting disparity between how the control of healthcare acquired infections (HAIs) is mathematically modelled and how it is implemented in reality. Constructed using the expert knowledge of microbiologists and clinicians, a stochastic, event-driven model is presented and used to assess realistic control scenarios for mitigating the transmission of C. difficile and reducing the burden of disease. Our methods apply to other HAIs and emphasise the paramount importance of interdisciplinary collaboration from the outset of model construction, through to its assessment of current practice and recommendations for future policy.

List of Attendees

David Allingham	School of Mathematical & Physical Sciences	Uni of Newcastle	David.Allingham@newcastle.edu.au
Andrea Babylon	Institute of Natural & Mathematical Sciences	Massey Uni	A.Babylon@massey.ac.nz
Nick Beeton	School of Zoology	Uni of Tasmania	nick.beeton@utas.edu.au
Andrew Black	School of Mathematical Sciences	Uni of Adelaide	andrew.black@adelaide.edu.au
Alex Cook	Saw Swee Hock School of Public Health, Department of Statistics and Applied Probability	National University of Singapore	stacar@nus.edu.sg
Miles Davenport	Centre for Vascular Research	Uni of NSW	m.davenport@unsw.edu.au
Stephen Davis	School of Mathematical & Geospatial Sciences	RMIT Uni	stephen.davis@rmit.edu.au
Tan Doan	Centre for Medicine Use & Safety	Monash Uni	tan.doan@monash.edu.au
Jessica Dunn	School of Mathematical & Geospatial Sciences	RMIT Uni	jessica.dunn@rmit.edu.au
Glenn Fulford	IHBI	QUT	g.fulford@qut.edu.au
Nic Geard	School of Population & Global Health	Uni of Melbourne	ngeard@unimelb.edu.au
Katie Glass	National Centre for Epidemiology & Population Health	ANU	kathryn.glass@anu.edu.au
Tony Green	School of Computer Science and Software Engineering	Uni of Wollongong	tgreen@uow.edu.au
David Harman	Biomedical and Physical Sciences Mathematics	Griffith Uni	David.Harman@griffithuni.edu.au

Jane Heffernan	Modelling Infection and Immunity Lab, Centre for Disease Modelling	York University	jmheffer@yorku.ca
Roslyn Hickson	School of Mathematical & Physical Sciences	Uni of Newcastle	Roslyn.Hickson@newcastle.edu.au
Alexandra Hogan	National Centre for Epidemiology & Population Health	ANU	alexandra.hogan@anu.edu.au
Simon Johnstone-Robertson	School of Mathematical & Geospatial Sciences	RMIT Uni	spjohnstonerobertson@gmail.com
Matt Keeling	Mathematics Institute, Department of Biological Sciences	University of Warwick	M.J.Keeling@warwick.ac.uk
Xing Lee	School of Mathematical Sciences	QUT	xing.lee@connect.qut.edu.au
Gerardo Martin Munzo de Cote	Public Health & Tropical Medicine	James Cook Uni	gerardo.martinmunozdecote@my.jcu.edu.au
Emma McBryde	Medicine	Uni of Melbourne	emma.mcbryde@mh.org.au
James McCaw	School of Population & Global Health	Uni of Melbourne	jamesm@unimelb.edu.au
Karen McCulloch	Institute of Natural & Mathematical Sciences	Massey Uni	k.mcculloch@massey.ac.nz
Carol McInerney	Mathematics	Uni of QLD	carol.mcinerney@uqconnect.edu.au
Shawn Means	Bioengineering	Uni of Auckland	s.means@auckland.ac.nz
Geoff Mercer	National Centre for Epidemiology & Population Health	ANU	Geoff.Mercer@anu.edu.au
Meksianis Ndii	School of Mathematical & Physical Sciences	Uni of Newcastle	meksand@gmail.com
Janka Petravic	Centre for Vascular Research	Uni of NSW	j.petravic@unsw.edu.au
Steve Petrie	School of Population & Global Health	Uni of Melbourne	spetrie@student.unimelb.edu.au

Mykola Pinkevych	Centre for Vascular Research	Uni of NSW	m.pinkevych@unsw.edu.au
Steven Riley	School of Public Health	Imperial College London	s.riley@imperial.ac.uk
Mick Roberts	Institute of Natural & Mathematical Sciences	Massey Uni	m.g.roberts@massey.ac.nz
Joshua Ross	Mathematical Sciences	Uni of Adelaide	joshua.ross@adelaide.edu.au
James Trauer	Centre for Population Health	The Burnet Institute	jtrauer@burnet.edu.au
Laith Yakob	School of Population Health	Uni of QLD	laith.yakob@uq.edu.au