Modelling and Analysis of Options for Controlling Persistent Infectious Diseases

David Price (*Debategraph)*
David Earn (*McMaster University*)
David Fisman (*University of Toronto*)
Jonathan Dushoff *(McMaster University*)

28 February – 4 March 2011

1. Introduction

The 5-day *BIRS* workshop on *Modelling and analysis of options for controlling persistent infectious diseases* (28 February to 4 March 2011) addressed some of the key public health policy themes raised during the BIRS *Modelling the Impact of Policy Options during Public Health Crises* BIRS workshop in 2008,[1] and gathered an interdisciplinary mix of mathematical modellers, clinicians and public health officials to explore these themes in the context of endemic infectious diseases.

Endemic infectious diseases have caused high levels of mortality and morbidity in human populations for centuries, and efforts to control them have a mixed record of success; with spatial and temporal fluctuations and evolutionary adaptation making the diseases hard to eliminate. A number of infections (including polio, measles, mumps, rubella, whooping cough) have been drastically reduced in large parts of the world (typically by vaccination) but remain persistently endemic (or resurgent) in several areas. Other infections (including malaria and tuberculosis) have been controlled in some areas by public-health measures, but continue to cause widespread morbidity and mortality over large parts of the world. Still other infections (including influenza and HIV) continue to defy control through

[1] Brauer, F., Feng, Z., and Glasser, J. BIRS Workshop Report: *Modelling the Impact of Policy Options during Public Health Crises*, 27 July – 1 August 2008.

vaccination and public-health measures and cause morbidity and mortality throughout the world. The only endemic pathogen to have been eradicated by human efforts so far is smallpox.[2]

Mathematical models have contributed to the understanding and control of infectious diseases for over a century and, with infectious diseases responsible for millions of deaths annually and their treatment and control imposing a significant economic burden, the need to develop efficacious models and to communicate the implications of these models to policy makers is as vital now as ever. Advances in knowledge and technology are creating new opportunities for progress: but many theoretical, clinical, practical and administrative challenges remain.

In gathering the group of mathematical modellers, clinicians and public health officials at the workshop, the organizers aimed to deepen mutual understanding of each community's insights and needs, and explore new strategies for disease control. To facilitate this, each of the first four workshop days began with a lecture introducing one of four practical challenges: disease control priorities, endgame strategies, economic constraints, and human behavioural factors. Shorter talks and discussions followed; highlighting recent progress in response to the relevant challenge for specific diseases and the models and analyses underpinning this progress. The fifth day was dedicated to open discussion of the topics explored across the first four days.

An overarching goal was that the insights emerging during the workshop should be shared with the broader mathematical, scientific, public health, and lay communities and continue to stimulate and inform community dialogue beyond the workshop. The organizers are accomplishing this in both traditional and innovative ways. The traditional methods included posting conference videos and documents to the BIRS website, presentation of summary slides by participants to their home institutions, and the publication of papers in peer-reviewed journals: the innovative method is described in detail below.

2. Mapping the BIRS Workshop

A five-day workshop elicits a vibrant, multi-dimensional dialogue that is difficult to compress accurately into a short, linear summary, and experiential energy and focus among the participants that are difficult to sustain and share beyond the workshop.

To address these challenges in an innovative way, this, the workshop organizers are experimenting with a new kind of web-based, visual dialogue mapping tool (Debategraph) that enables the content and structure the group's conversations

[2] Eradication is the reduction of an infectious disease's prevalence in the global host population to zero. Elimination refers either to the reduction of an infectious disease's prevalence in a regional population to zero, or to the reduction of the global prevalence to a negligible amount.

and thinking to be mapped collaboratively by the participants before, during and after the workshop and then shared, via the web, for other participants to explore and build upon the conversation.

Debategraph has been used in public policy projects by, amongst others *the White House*, *the UK Foreign Office*, *the European Commission* *and* *CNN*, and its use in the context of the BIRS workshop can be seen as part of the wider experiments underway with the open science movement. As noted in a recent Nature blog post:

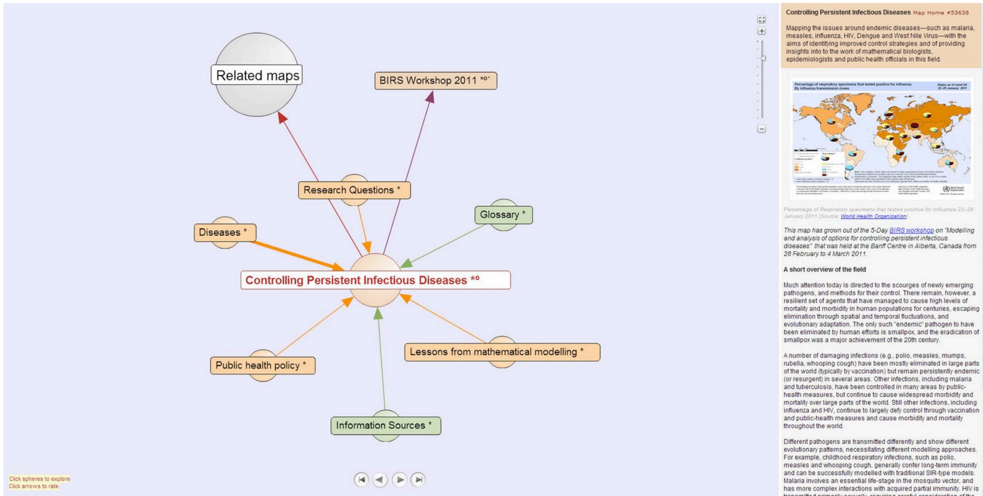
> *"How we read, write, and communicate science is changing profoundly under the influence of new technologies. In several fields within and outside of computer science, models, tools and standards are being developed that aim to enhance, enable or entirely replace formerly ingrained forms of scientific communication. Scientists, publishers, and vendors in various disciplines are developing methods and tools to improve the process of creation, reviewing and/or editing of scientific content; working on technologies and techniques to interpret, visualize, or connect scientific knowledge more effectively; and formulating concepts, tools, standards, and techniques for sharing multimodal and research data. These developments are currently taking place in disparate and disconnected domains, including computational linguistics, bioinformatics, information science areas like the semantic web or web technologies* in general, social sciences, and computer-human interface studies."[3]

While the technology and thinking in this area remain nascent, the potential to engage interconnected networks of scientists, researchers and wider stakeholders in new kinds of transparent, systematic dialogue, practice and inquiry is tantalizing—and the potential to shift the mode of discourse from the limited historical form and conventions of static, linear papers towards more open, dynamic and collaborative editable graphs of ideas and arguments is intriguing.

Debategraph is an early exemplar of the new family of tools that are starting to emerge in this domain, and Debategraph's adoption by policy makers and mass media organizations makes it an apt choice for the issues addressed by the BIRS workshop. The tool's main characteristics, and the ways in which these characteristics were applied in the workshop are outlined below.

Figure 1: The BIRS Debategraph –Controlling Persistent Infectious Diseases

[3] http://blogs.nature.com/eresearch/2011/07/04/towards-executable-journals

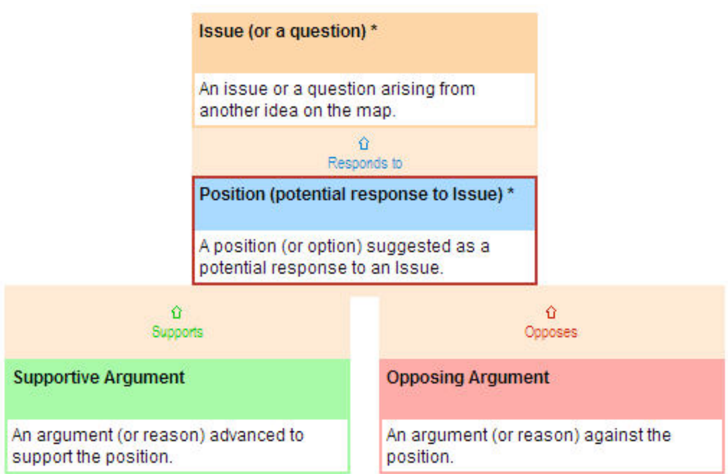


In essence, the map/graph building process in Debategraph involves four steps:

1. breaking down the subject under discussion into discrete ideas;
2. figuring out the relationships between those ideas;
3. expressing the ideas and relationships visually; and
4. reiterating steps 1-3 to improve the map as understanding and consensus develop.

Ideas are visualized as thought bubbles or boxes and relationships between ideas are visualized by directed arrows, with a distinctive colour scheme, reflecting types of ideas and types of relationships, layered across the visualization so that the implied structure and meaning of the network of ideas can be interpreted at a glance.

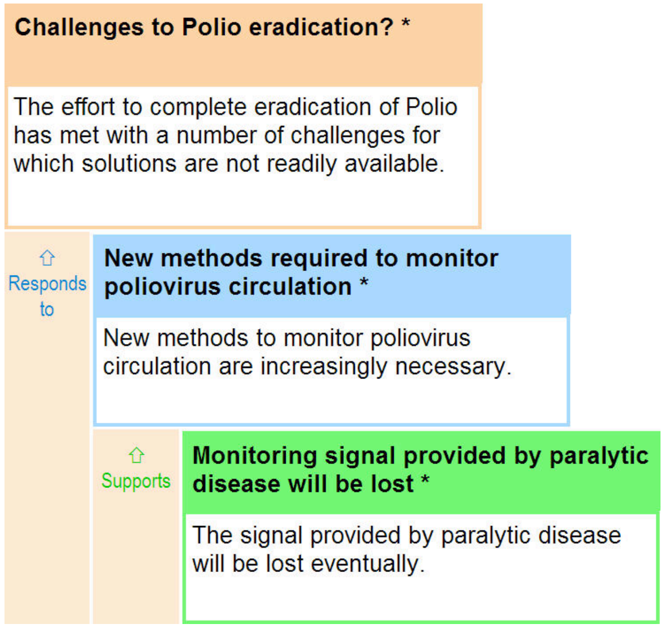
Figure 2: The basic building blocks of a map



For example, Figure 2 (above) shows the core set of building blocks—Issues (orange) raised, Positions (blue) suggested in response to these Issues, and Supportive (green) and Opposing (red) Arguments advanced for and against the

Positions—and Figure 3 (below) illustrates how these building blocks have been applied in a small strand of the BIRS map:

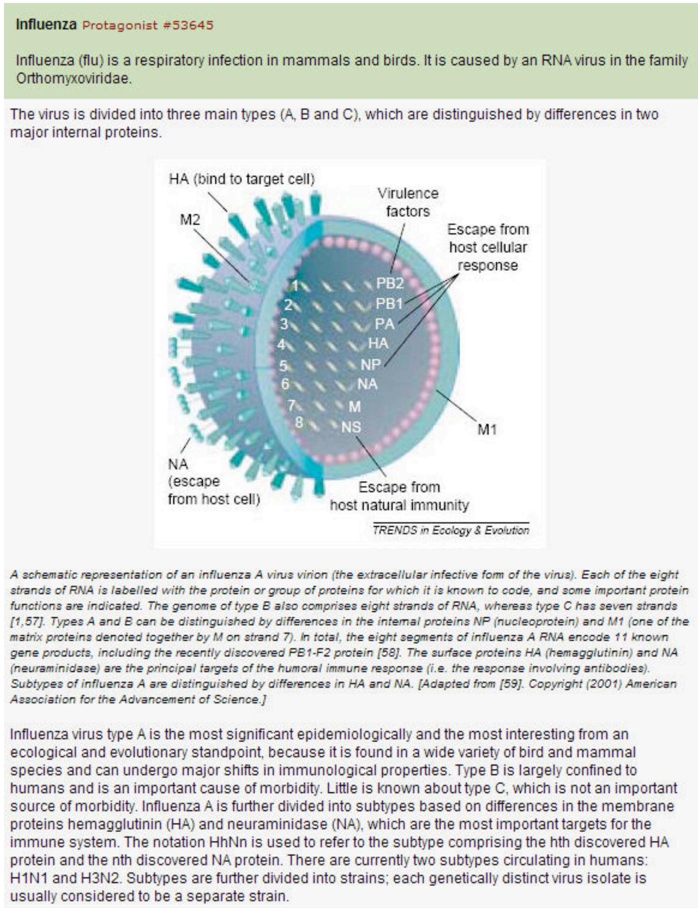
Figure 3: Exploring challenges to the eradication of Polio



In Figure 3 (above), a question is asked about the remaining challenges to the eradication of polio. A potential challenge to the elimination of polio is proposed (that new monitoring methods will need to be developed to achieve eradication), and a reason is offered in support of this challenge (that the current signal from the paralytic disease will be lost).

Videos, images, charts, tables, detailed text, documents, files citations and comments can be added to each idea, and ideas can be cross-linked to other ideas on the same or different maps. All members of the group can add new ideas and edit and rate existing ideas (with visual cues signalling which ideas have the strongest weight of support).

Figure 4: Each idea can be articulated in depth



Influenza Protagonist #53645

Influenza (flu) is a respiratory infection in mammals and birds. It is caused by an RNA virus in the family Orthomyxoviridae.

The virus is divided into three main types (A, B and C), which are distinguished by differences in two major internal proteins.

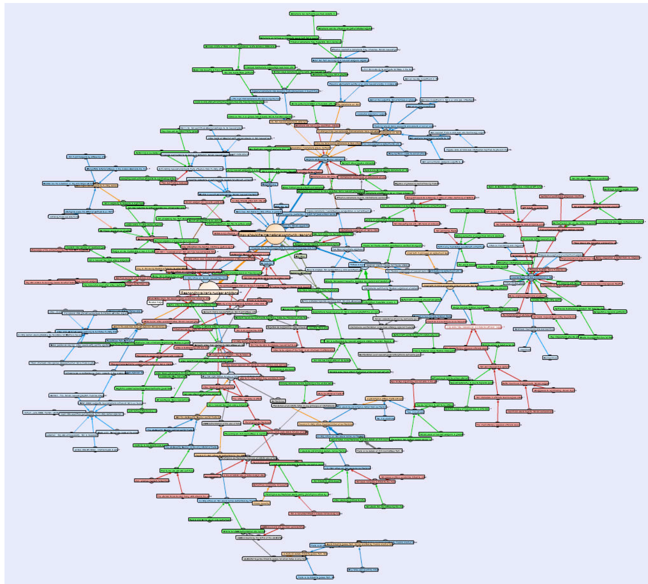
A schematic representation of an influenza A virus virion (the extracellular infective fom of the virus). Each of the eight strands of RNA is labelled with the protein or group of proteins for which it is known to code, and some important protein functions are indicated. The genome of type B also comprises eight strands of RNA, whereas type C has seven strands [1,57]. Types A and B can be distinguished by differences in the intemal proteins NP (nucleoprotein) and M1 (one of the matrix proteins denoted together by M on strand 7). In total, the eight segments of influenza A RNA encode 11 known gene products, including the recently discovered PB1-F2 protein [58]. The surface proteins HA (hemagglutinin) and NA (neuraminidase) are the principal targets of the humoral immune response (i.e. the response involving antibodies). Subtypes of influenza A are distinguished by differences in HA and NA. [Adapted from [59]. Copyright (2001) American Association for the Advancement of Science.]

Influenza virus type A is the most significant epidemiologically and the most interesting from an ecological and evolutionary standpoint, because it is found in a wide variety of bird and mammal species and can undergo major shifts in immunological properties. Type B is largely confined to humans and is an important cause of morbidity. Little is known about type C, which is not an important source of morbidity. Influenza A is further divided into subtypes based on differences in the membrane proteins hemagglutinin (HA) and neuraminidase (NA), which are the most important targets for the immune system. The notation HhNn is used to refer to the subtype comprising the hth discovered HA protein and the nth discovered NA protein. There are currently two subtypes circulating in humans: H1N1 and H3N2. Subtypes are further divided into strains; each genetically distinct virus isolate is usually considered to be a separate strain.

The ultimate aim is to weave all of the salient ideas, arguments, evidence and citations of which anyone in and beyond the group is aware into a single rich, transparent, dynamic structure—in which each idea and argument is expressed just once—so that anyone can explore the resulting knowledge base quickly and gain a good sense of the key issues and the perceived merits of the potential responses.

While many different ideas types and relationships are available in Debategraph—including causality, consistency and formal logic—the core dialogic triad described above (of Issues, Positions, and Supportive and Opposing Arguments) can be combined multiple times to build large, comprehensive maps (Figure 5).

Figure 5: Large maps evolve from the combination and re-combination of small strands of arguments



As the map evolves, changes to the map are flagged to the community via email and RSS feeds—and anyone who spots a gap and identifies a new idea can add the idea to the map immediately for the whole group to see.

Figure 6: Alerts to your phone when an idea updates

In essence, by externalising and structuring thought in this mutable way, the maps begin to augment the individual and group ability to think through complex, interrelated issues; helping the participants and readers to overcome the cognitive constraints of short-term memory and sub-optimal group processes such as groupthink and homophily—and to do so in an often playful, creative and engaging way.

The maps allow individuals and groups to apply their minds to the full set of ideas rather than a partial subset, and by reasoning transparently and iteratively help the group to reason rigorously, with each idea always open to direct challenge and improvement. In much the same way as a mediator seeks to create a physical space in which conflict can be explored and resolved, the interactive maps provide a networked context in which the conflicting values and interests, of multiple stakeholders can be surfaced and addressed openly and in an explicitly reasoned way.

Sharing understanding in a structured and transparent form also helps each participant to see that his or her perspective has been heard and represented accurately in the appropriate context, which helps to build trust and ensure that the maps evolve towards a full and fair reflection of the subject under consideration.

Furthermore as each idea only has to be stated once openly on the map, the mapping process can be highly time-efficient compared to working with a large body of static documents (across which many ideas will typically be repeated many times). Group members can move quickly through the top-level structure of the map and identify both the specific strands that need their attention and the relationships of those strands to the rest of the material.

Finally, documenting the reasoning behind a team's thinking and decisions helps to bring greater clarity and accountability to the group's analysis, decision making, and actions, which, in turn helps the group and the wider community to identify and learn from any mistakes and to improve the decision making process over time.

3. Overview of the BIRS Workshop Discussions

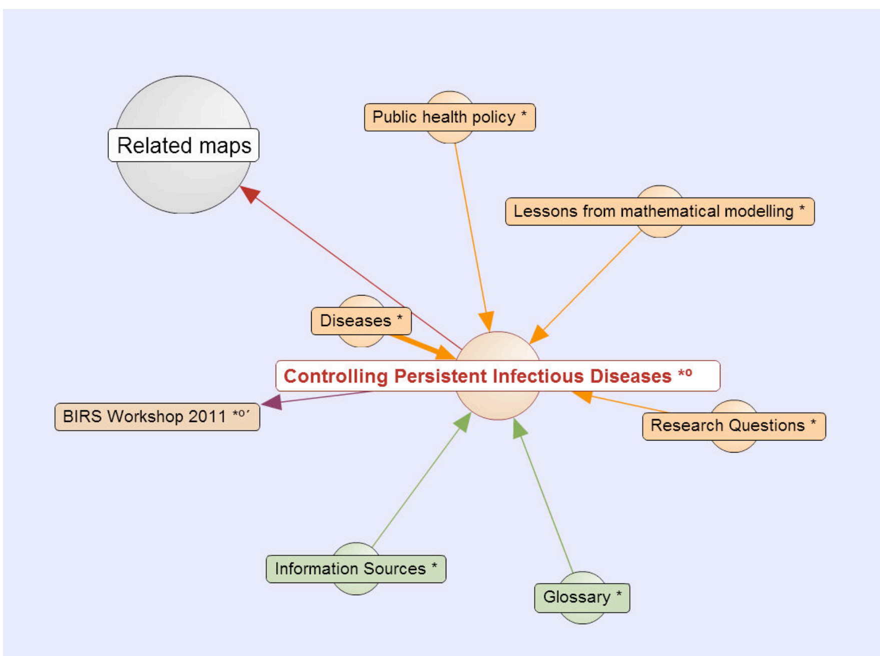
The map was displayed throughout the workshop on a second screen to the right of the main presentation screen Figure 7); with a visual facilitator, David Price (Debategraph's co-founder), mapping the presentations and group conversation as they unfolded.

At the same time, group members with laptops were able to log-in, add to, edit, comment on, restructure and rate the ideas live as they were being discussed.

Figure 7: Mapping the discussion live during the workshop. David Price (right) builds and displays a map as David Earn talks. Other members contributed to the same map in real time during lectures.

Across the duration of the workshop, the top level structure of the map evolved towards the form show in Figure 8 (below), with a glossary, information sources and a cross-link to the workshop preparatory map accompanied by four main discursive branches: Diseases, Public Health Policy, Research Questions, and Lessons from Mathematical Modelling.

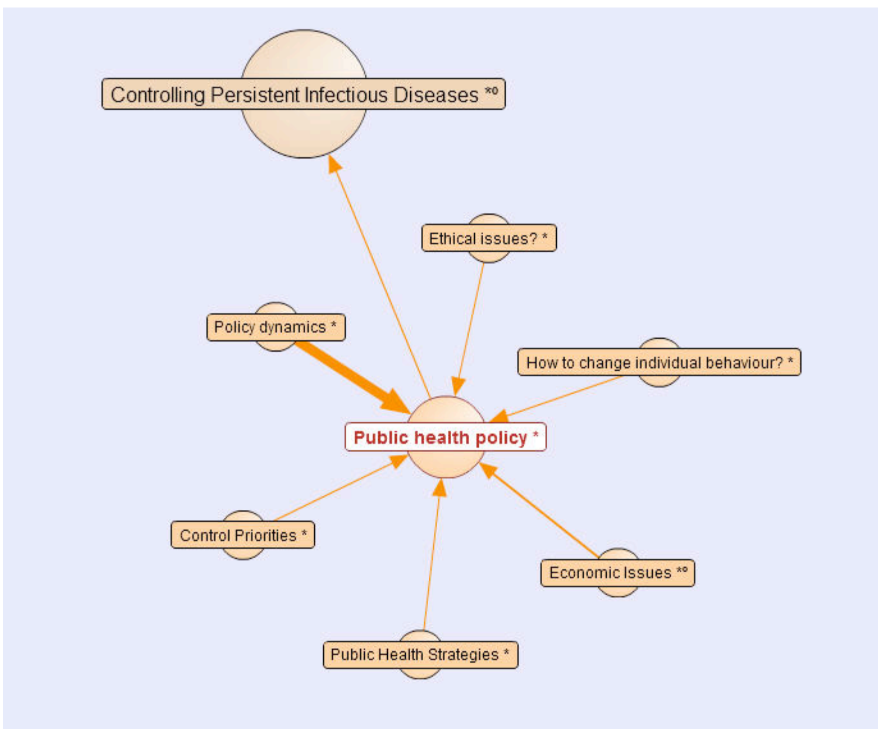
Figure 8: Top level issues addressed at the BIRS Workshop



The Disease branch of the map enables the participants and readers explore the workshop presentations and discussion by disease (Cholera, Clostridium Difficile, Dengue, HIV, Influenza, Lyme disease, Malaria, Measles, MRSA, Neglected Tropical Diseases, Pertussis, Polio, Rabies, Smallpox, Syphilis, TB, and the West Nile Virus), or by categories of disease (e.g., acute diseases, viral diseases, diseases with an environmental reservoir, diseases with pandemic potential, diseases spread by specific forms of transmission). The health policy issues addressed during the workshop included:

- **Policy dynamics**: What do policy makers want from modellers? Who are the key audiences for the messages from modellers? What role does the media play and how can modellers ensure that media communication is appropriate and effective? And how to overcome the current and detrimental disconnect between policy makers and modellers?.
- **Economic issues**: Externalities in public health; the need for, and benefits of, improving health-related infrastructure through investment; corruption and poor governance as drags on improvement of public health; ways to align human behaviour with the public good; the correlation between wealth and health; cost-effectiveness of various interventions; and the use of electronic "prediction markets" (such as the Iowa Electronic Health Markets, http://iehm.uiowa.edu/iehm/index.html) as alternative tool for public health surveillance.

Figure 9: Public Health Policy issues explored at the BIRS Workshop



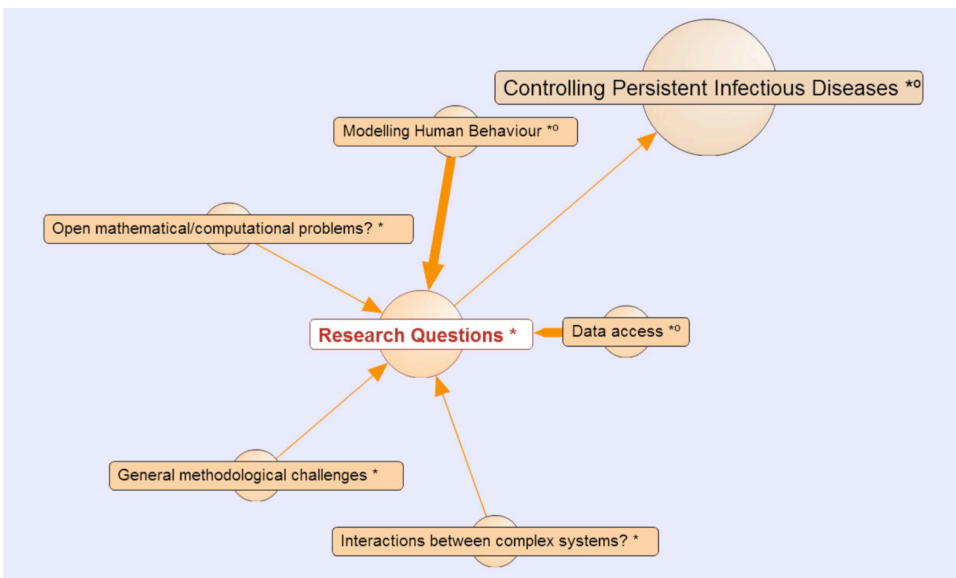
- **Control priorities**: How to balance different control priorities (reduction of illness, reduction of death, prevention of spread, prevention of vaccine/drug escape); the potential utility of conjoint analysis as a tool for prioritisation; and the need for better data collection.
- **Ethical Issues**: health inequalities at a national and global scale; the trade-off between individual and population level interests; the social implications of switching from a policy strategy of elimination to one of disease management, and public health as a basic human right.

- **Optimum strategies**: Identifying whether an eradication, elimination or management strategy is pragmatic for a given disease and/or location, and the growing importance and utility of dynamically-crafted public health strategies
- **Behavioural change**: Whose behaviour should we be trying to change (e.g. people who are infected, susceptibles, public health officials, politicians, journalists) and how can we accomplish this behavioural change? Top down edicts from public health authorities may be counterproductive—how do we change people's perception of what is valuable, empower them to find the answers for themselves, use social marketing tools used in other disciplines, etc.

The key research questions addressed by the workshop included:

- improving access to existing data sources (many of which are being collated at the International Infectious Disease Data Archive (IIDDA);
- the limitation of existing surveillance methods, and the desirability of involving modellers in the design and improvement of current surveillance and data gathering techniques;

Figure 10: Research questions discussed at the BIRS Workshop



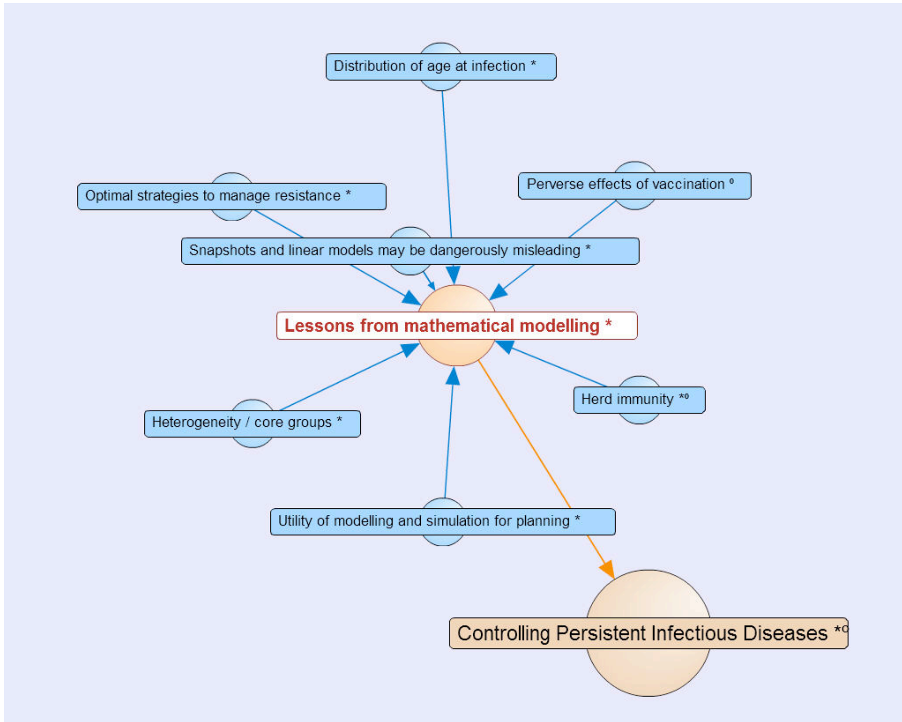
- the potential utility of novel surveillance tools (such as Google Flu Trends);
- the challenges of modelling human behaviour (including the difficulty of untangling and pinpointing the behavioural component amid many variables and degrees of freedom);
- the degree to which models can provide insights into interactions between complex systems—e.g. disease systems, systems of governance, and multinational aid organizations—that enhance the likelihood of successful disease control, and the need to avoid the temptation to always adopt a narrow disease-by-disease focus; and,
- whether the modelling and policy community is too focused on R_0 in particular—which policy makers like (as reducing the characteristics of

disease to a single number makes it easier for policy makers to comprehend and communicate what is happening), and which mathematical epidemiologists like (because of the opportunities afforded to prove things about the threshold)—and on quantitative prediction in general. Should modeling be rebranded as a toolbox for the management of uncertainty, rather as a source of reliable predictions?

Finally, the workshop participants thought it might be helpful, to help communicate the character and significance of the field to a wider audience, to identify some of the major contributions from mathematical modelling to field of public health so far; namely:

- **Disease transmission thresholds:** Infectious diseases need to create at least one case per case to persist in a population. This implies that a *finite* reduction in risk could lead to a disease going extinct at the population level, even if some or all individuals remain susceptible to some degree, a phenomenon known as "herd immunity".
- **Distribution of age at infection**: Modelling has provided key insights into factors underlying the age distribution of infected individuals, and how this may change as an epidemic spreads or as risk factors change. Understanding this link has proved critical in particular for avoiding the possibility of "perverse outcomes" in public health interventions: an intervention that weakens but does not eliminate disease transmission will typically increase the average age of infected individuals; in some cases this can lead to greater total burden of disease.
- **Heterogeneity / core groups**: A small "core" group of disease transmitters may account for a large percentage of cases; with an 80/20 rule of thumb suggesting that 20% of the people in a community may contribute 80% of the contacts (disease, infection, susceptibility, etc.) and vice versa.
- **Optimal strategies to manage resistance**: Mathematical modelling has helped to identify optimal strategies for managing resistance. For example, the adoption of combination therapy for malaria.

Figure 11: Key Lessons from Mathematical Modelling so far



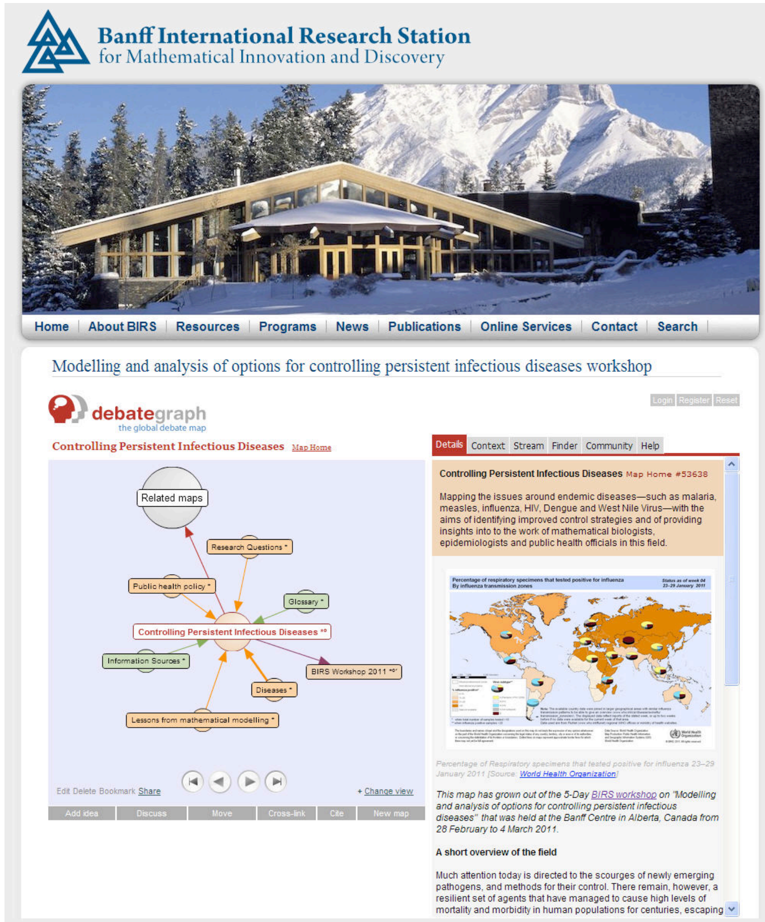
- **Snapshots and linear models may be dangerously misleading**: Snapshots and linear models were, for a long time, the models of choice for public health officials; as they tend to be more accessible to the "common sense" understanding of non-mathematical policy stakeholders. However, natural systems are often better understood—and therefore offer a sounder basis for policy decisions—as dynamic, non-linear systems. For example, linear/snapshot models may miss the rebound/delayed effects arising from the elongation of inter-epidemic period and the build up of susceptibles during periods of lowered vaccination rates.
- **Utility of modelling and simulation for planning**: Mathematical modelling and simulation can provide a more effective basis for public health planning and decision making.

4. Continuing the BIRS Dialogue Online

As noted earlier, one of the attractions of using web-based, collaboratively editable tools like Debategraph is that the dialogue and shared understanding can continue to build online after the workshop; both for the workshop attendees and for the wider public health stakeholders.

Since the workshop concluded, the map has continued to grow—including material, for example, from the Gates Foundation and BIREME (a PAHO Specialized Center for Latin America)—and now encompasses over a thousand ideas.

Figure 12: Widening the Dialogue online after the BIRS workshop



The full map, including all of the editing functionality, is embedded on the BIRS website here[4]—and is freely available to embed on the blogs and websites of other interested organizations—and readers of this report are welcome and encouraged to read and explore the map in depth, and to join the continuing dialogue here.

[4] http://www.birs.ca/events/2011/5-day-workshops/11w5133/debategraph