

Building capacity for mathematical modelling of infectious disease

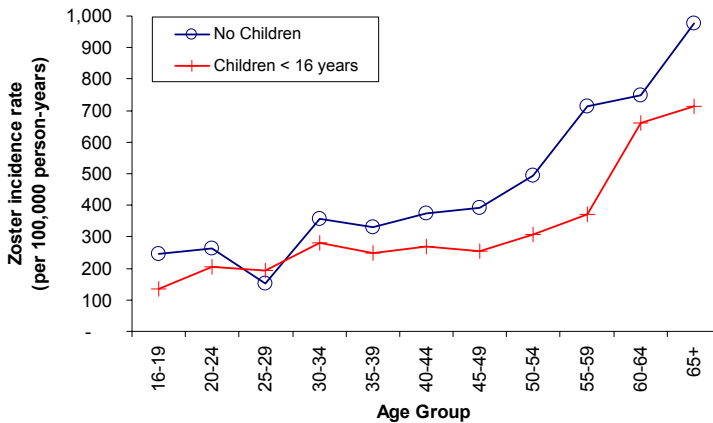
Progress in Australia and opportunities
through Universitas 21

Professor Terry Nolan
School of Population Health



Why use mathematical models?

- Experiments not possible
- No time to wait for 'natural experiments'
- Population effects beyond those immediately affected
 - Herd effects
 - Removal of natural infection benefits by vaccines



Thomas et al, Lancet 2002. Analysis of 1 year prospective survey of morbidity in GPs (MSGP4)

Lack of boosting and zoster

- Epidemiologic evidence shows that contact with children who have chicken-pox protects against zoster in adults.
- Immunologic evidence shows that intimate exposure to children with varicella boosts VZV-specific CMI in seropositive adults.
- Therefore, consider possible effect of reduced wild virus boosting of naturally infected individuals if high vaccine uptake is achieved in children.
- Recent modelling studies predict that the lifetime risk of zoster will be over 50% in those aged 10-44 years at the introduction of mass vaccination.

Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox

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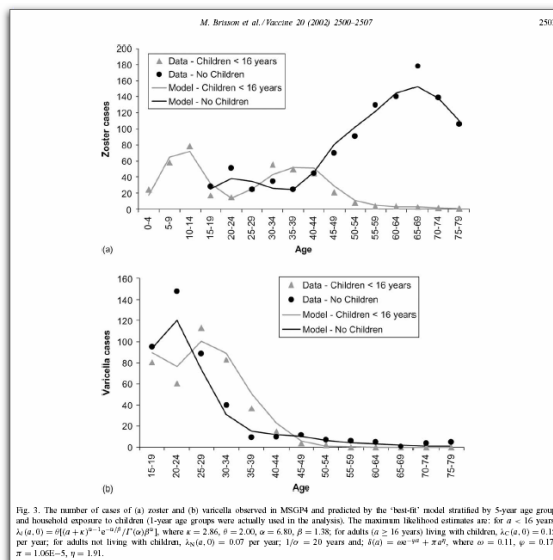
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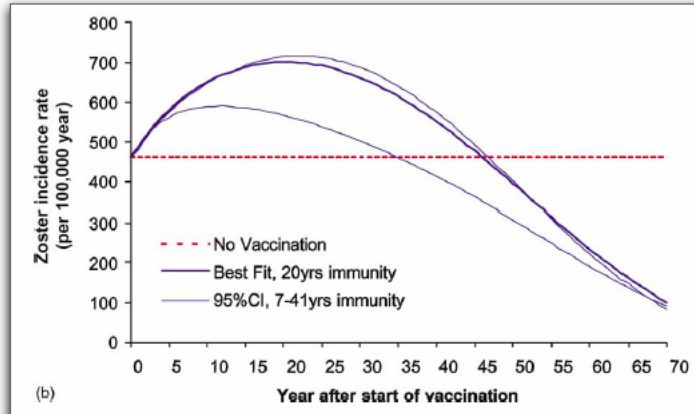
Received 22 October 2001; received in revised form 8 March 2002; accepted 11 March 2002

Abstract

We present data to confirm that exposure to varicella boosts immunity to herpes-zoster. We show that exposure to varicella is greater in adults living with children and that this exposure is highly protective against zoster (Incidence ratio = 0.75, 95% CI, 0.63–0.89). The data is used to parameterise a mathematical model of varicella zoster virus (VZV) transmission that captures differences in exposure to varicella in adults living with and without children. Under the ‘best-fit’ model, exposure to varicella is estimated to boost cell-mediated immunity for an average of 20 years (95% CI, 7–41 years). Mass varicella vaccination is expected to cause a major epidemic of herpes-zoster, affecting more than 50% of those aged 10–44 years at the introduction of vaccination. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Varicella zoster virus; Vaccination; Modelling



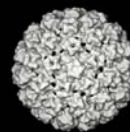


Left shift in age of zoster

- May actually be (net) beneficial
- Less severe episodes at younger age
- May have higher risk of second episode but each may be less severe.
- Lower net burden possible.
- Will vaccination of naturally infected adults prevent zoster?
 - US Veterans Cooperative Study results recently presented at ESPID
 - Enrolled 38,546 aged 60y+
 - High release titre VZV vaccine vs placebo
 - Good efficacy (approx. 65%) against incidence and severity (post-herpetic neuralgia)

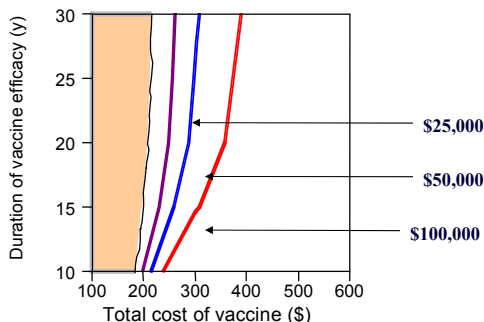
HPV vaccine soon available

- Two VLP-based HPV vaccines in Phase III (for CIN 2/3 outcomes) after excellent Phase II results in relation to protection against HPV persistence.
- Efficacy for cervical cancer prevention still to be demonstrated. Won't know real efficacy against cancer for 30 years or more.
- Durability of efficacy unknown, crucial for booster frequency and possible infant delivery
- Cervical cancer screening programs will not be able to cease, although they would theoretically become less cost-effective as fewer cases occur if vaccine uptake high.
- Modelling vaccine impact against modification in screening needed to guide policy



Two-way Sensitivity Analysis Varying Duration of HPV Vaccine Efficacy and Total Cost

(Direct Medical Costs Only)



Population modelling of pertussis

- Adult boosting every 10 years should reduce number and severity of adult pertussis infections
- But, mathematical modelling suggests that adult boosting will only produce modest reduction in pertussis in infants and children through herd effects.



Simulations of pertussis epidemiology in the United States: effects of adult booster vaccinations

Herbert W. Hethcote*

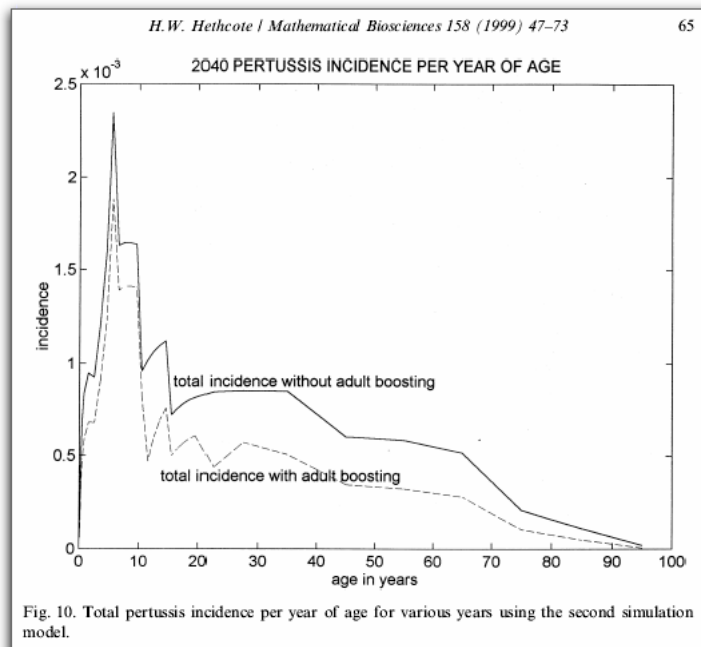
Department of Mathematics University of Iowa, Iowa City, Iowa 52242, USA

Received 3 August 1998; received in revised form 6 January 1999; accepted 6 January 1999

Abstract

An expanded pertussis (whooping cough) vaccination program which includes adult boosters every 10 yr is studied using computer simulations of two models. These age-structured pertussis transmission models include waning of both infection-acquired and vaccine-induced immunity, and vaccination of children corresponding to the vaccination coverage since 1940. Adult vaccinations cause a larger boost in the immunity level in the second model than in the first model. In the simulations the addition of adult pertussis booster vaccinations every 10 yr is beneficial in reducing adult incidence, but causes only modest reductions in the incidence in infants and young children. These simulations suggest that a careful cost effectiveness analysis is needed before implementation of an adult pertussis vaccination program. © 1999 Published by Elsevier Science Inc. All rights reserved.

Hethcote population adult pertussis booster model



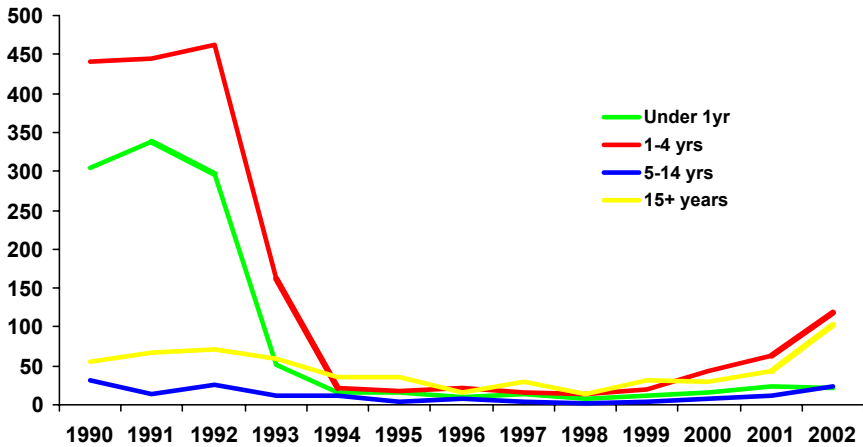
What about a 'cocoon' strategy to protect against infant pertussis deaths?

- Idea is to vaccinate all family members of expectant mothers (including extended family)
- Protect the newborn by immunising all those who have contact before the age of 6 months (when infant primary course should be completed)
- Epidemiologic evidence suggests that this could work
- However, not yet demonstrated or evaluated. France has introduced this as a national recommendation.
- Renewed interest in neonatal immunisation with acellular vaccines, studies in progress.

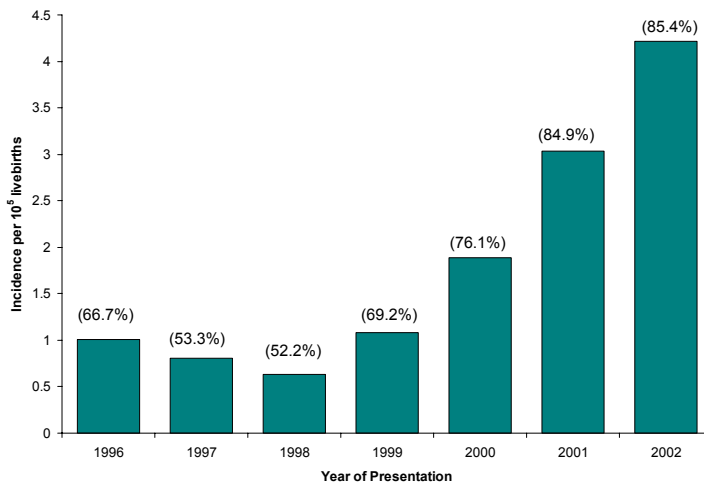
Invasive Hib Infections in the UK, 1990-2002

- Hib vaccine successfully introduced October 1992 at 2, 3, 4 months (no booster) with one year catch-up (under 5 years)
- Rising incidence of infections around 2000, mainly in immunised children
- Epidemiologic studies increased the understanding of declining vaccine efficacy
- These data were important in parameterising and validating models of Hib infection and immunity

Invasive Hib infections by age group, 1992-2002, England and Wales



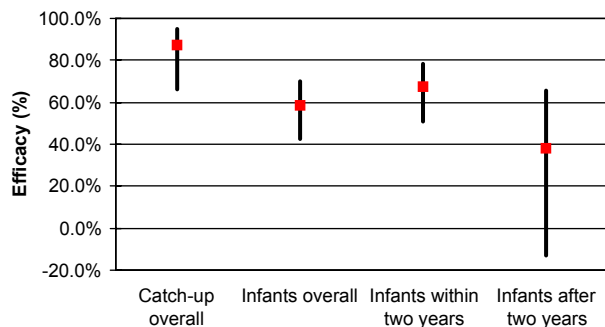
Invasive Hib incidence in the United Kingdom per 100,000 children under 5 years of age (% of all reports following three doses of vaccine, by year)



Hib Vaccine Use in Britain

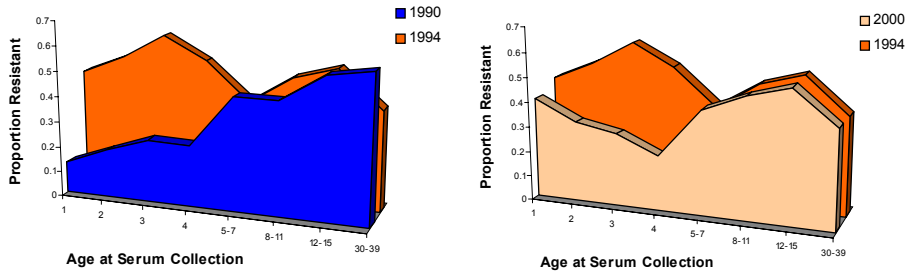
- Direct protection following the 2, 3, 4 month infant primary course lower than expected: 61% for 2 yrs, 27% thereafter
 - (Ramsay ME et al 2003 JID)
- Low efficacy masked by initial 'catch-up' campaign effect
 - (Trotter CL et al 2003 Lancet)
- Increased risk of vaccine failure in recipients of less immunogenic DTaP-Hib in 2000-2001
 - (McVernon J et al 2003 Lancet)

Hib Vaccine Efficacy in Britain, 1992-2001



Ramsay ME, McVernon J, Andrews N, Heath PT, Slack MPE. *J Infect Dis* 2003; **188**: 481-5. Estimating *Haemophilus influenzae* type b vaccine efficacy in England and Wales by use of the screening method.

Population Immunity to Hib in Britain, 1990-2000



Trotter CL, McVernon J, Andrews NJ, Burrage M, Ramsay ME. Antibody to *Haemophilus influenzae* type b after routine and catch-up vaccination. *Lancet* 2003; **361**: 1523-4.

DTaP-Hib and Risk of Vaccine Failure

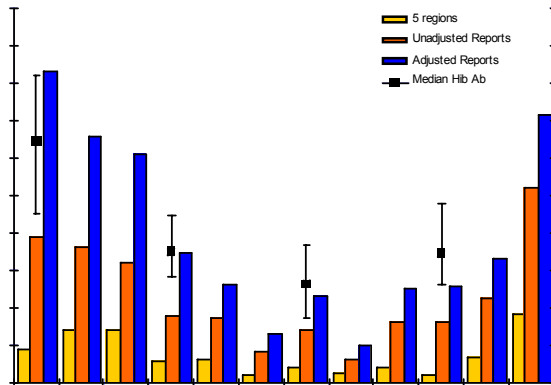
British 2, 3, 4 month schedule without booster

No doses of Infanrix-Hib received within 3 dose primary course

	0	1	2	3
Cases	24	15	17	55
Controls	1223	783	612	1216
Conditional Odds Ratio		1.1	2.2	6.35
(95% CI)		(0.6-2.2)	(1.1-4.6)	(3.1-13.2)
OR for trend 1.87 (1.46-2.40) per dose ($p < 0.0001$)				

McVernon J, Andrews NJ, Slack MPE, Ramsay ME. Risk of vaccine failure after *Haemophilus influenzae* type b (Hib) combination vaccines with acellular pertussis. *Lancet* 2003; **361**: 1521-3

Adult Hib Infections and Waning Herd Immunity in Britain, 1990-2002



McVernon J, Trotter CL, Slack MP, Ramsay ME. Trends in *Haemophilus influenzae* type b infections in adults in England and Wales: surveillance study. *BMJ* 2004; 329; 655-8.

Questions addressed by the Hib Model

- Examination of key assumptions about:
 - Degree and duration of natural and vaccine induced immunity
 - Relative protection against carriage/disease
 - *How might changing vaccine use impact on direct and indirect protection?*
- How might interruption of Hib transmission affect maintenance of population immunity in the longer term?
 - *How are these effects influenced by social mixing assumptions?*

Model Conclusions

- No resurgence of Hib infections without very low direct efficacy of immunologic memory ($\approx 35\%$)
- Risk of invasive disease exquisitely age dependent
- Poorly immunogenic vaccine 'exposed' susceptible infants to risk of disease
- Catch-up campaign produced large transient effects in older unimmunised cohorts
- Within-age group mixing important for Hib transmission

McVernon, unpublished.

Future Hib Studies

- Investigation of the time course of transients in other populations
 - Netherlands
 - No catch up campaign
 - Routine booster dose, same vaccine throughout
 - Rise in paediatric and adult cases in 2002
 - Australia
 - Catch-up campaign
 - Routine booster dose
 - Change to less immunogenic vaccine in 2000

National program in mathematical modelling of IDs

- Collaboration between 5 Universities
 - **University of Sydney**
 - National Centre for Immunisation Research and Surveillance
 - **Australian National University**
 - National Centre for Epidemiology and Population Health
 - **University of Melbourne**
 - School of Population Health
 - Department of Medicine and Victorian Infectious Disease Service
 - **University of New South Wales**
 - National Centre in HIV Epidemiology and Clinical Research
 - **Curtin University**
- Lead investigators
 - Niels Becker (Math), Graham Brown (ID), Raina MacIntyre* (Epi), Matthew Law (Math), Terry Nolan (Epi), Aileen Plant (ID)
- Funded by National Health and Medical Research Council (NHMRC) for five years

Research Objectives

1. Establish a comprehensive program of research, based on mathematical modelling, to aid the understanding of and provide policy support for the control of IDs, now and well into the future, through mentoring and career development of talented post-doctoral researchers.
2. Integrate mathematical modelling with policy and public health service delivery.
3. Complete about 20 specific research studies under three national major ID control themes.
4. Achieve research outcomes that will establish an international reputation for the team.

Capacity Building Aims

1. Develop high-level technical capacity in mathematical modelling of IDs in Australia, with a focus on research that informs health policy.
2. Appoint six outstanding team investigators to positions in the health sector and develop them into capable, independent public health researchers.
3. Meet immediate, existing policy needs at state, national and global levels.
4. Develop a prominent and experienced research team capable of sustaining international quality research into the future, within the collaboration but also with government and academia.
5. Establish a Network of Infectious Diseases Modellers of Australia (NIDMA) as body of national expertise, peer support and a means of ongoing communication and collaboration in ID modelling.
6. Develop a critical mass of modelling expertise that will be sustainable long-term, and that will expand into modelling of chronic and other non-infectious diseases after the lifetime of the grant.

Research themes

- *Theme 1:*
 - **Population threats from infectious diseases**
 - Bioterrorism and emerging IDs (preparedness and control)
 - group project
 - Nosocomial infections
 - Control of drug resistance

Research themes

- Theme 2:
Control of existing infectious diseases
 - Optimal policy for mass vaccination
 - HPV, HSV2, hepA, pertussis
 - Monitoring vaccination programs
 - Hib, MenC, Pneumo, hepB etc
 - Effect of behavioural changes
 - HepC, HIV, effect of anti-retroviral therapy

Research themes

- Theme 3:
New methods to use data to improve transmission models
 - Research into data requirements
 - e.g. household structure
 - Social and behavioural data
 - Transmission matrices (social mixing)
 - Surveillance and serological data

TABLE D1: The Research Program		
THEME 1. Population threats from infectious diseases		
1. Bioterrorism and emerging infectious diseases	1.2 Nosocomial infections	1.3 Control of drug resistance
(a)* Optimal strategies for control of: (i) SARS and new infections (ii) Deliberate smallpox attack (iii) Influenza pandemic	(a) Best practice strategies for control of nosocomial infections (MRSA, VRE)	(a) Informing computerised clinical decision support tools for antibiotic prescribing
(b) Economic modeling of control strategies for emerging IDs and bioterrorism		(b) Effect of using antibiotics in animal feed
(c) Preparedness for an influenza pandemic		(c) Effective use of antivirals for HIV and influenza; focus on drug resistance
THEME 2. Control of existing infectious diseases		
2.1 Optimal policy for mass vaccination	2.1 Monitoring vaccination programs	2.3 Effect of behavioural changes
(a) Assessing the public health impact of vaccination programs against (i) varicella, (ii) hepatitis A, (iii) HPV, (iv) pertussis	(a) Meningococcal C vaccine program, including herd immunity, strain replacement, adverse events, changing targets for vaccination	(a) HIV transmission, antiretroviral treatment and sexual behaviour among homosexual men
(b) Economic evaluation of vaccine program options	(b) Monitoring elimination of (i) measles, (ii) Hib	(b) HCV transmission in injecting drug users, including economic modeling
(c) Vaccine efficacy for transmissible diseases	(c) Using serological data to monitor vaccination programs	(c) Transmission models based on social contact patterns
THEME 3. New methods to use data to improve transmission models		
3.1 Research into data requirements	3.2 Social and behavioural data	3.3 Surveillance and serological data
(a) Design of studies to estimate transmission rates within households	(a) Estimating contact rates between social groups	(a) Estimating transmission rates from serological data
(b) Assessing the merits of sentinel surveillance data for estimation	(b) Estimating transmission rates for sexually transmitted diseases	(b) Estimating trends from surveillance data

Datasets

- Australian Childhood Immunisation Register (ACIR)
- National serosurvey
- NNDSS (Nosocomial dataset)
- Australian Institute of Health and Welfare (AIHW)
- National HIV surveillance data
- Enhanced surveillance datasets
- Data arising from purpose-designed research studies

Training

- **Field placement of TIs:** rotating the TIs across the participating centres
- **Training from diverse and complementary expertise:** Each Lead Applicant brings unique expertise in mathematical modelling, applied mathematics and statistics, epidemiology, clinical ID, public health, emerging infections, health policy and health service delivery.
- **Training by external experts:** In addition to training by LAs, international experts Dr James Noakes and Dr Graham Medley from the University of Warwick, UK and Dr Nigel Gay from the Health Protection Agency, UK, will train the TIs.
- **Research and training residency:** A rotating short-term position filled by international experts in modeling or other expertise considered essential to the project. This will ensure the group keeps abreast of the latest developments, and promotes collaborative links with leading overseas research teams, Australian policy makers and individuals with specific research expertise.
- **Workshops:** Twice per year intensive training and to promote collaboration between all TIs and LAs.
 - ID epidemiology;
 - mathematical transmission models;
 - modeling for SARS and emerging infections;
 - transmission between and within social networks;
 - modeling of HIV and other blood-borne diseases;
 - computing and modeling –including software (Model Maker, Dyno);
 - economic assessments from modeling results; translating modeling results to public health policy and outcomes .
- **Practical placements in health service delivery environment:** TIs will complete a 3-month placement at a centre engaged in direct public health service delivery, such as PHLS, Colindale and state health departments.
- **Networking:** Innovative information technology will be used to build a national network that results in synergistic research outcomes from the group.
- **Research collaborations:** All TIs will work together on a group project, and potentially collaborate on other specific projects
- **Authorship of joint book:** The TIs and LAs will jointly author a book (edited by LA Becker) on applications of mathematical modelling in infectious diseases, based on their research projects.
- **Mentoring:**

Network of Infectious Diseases Modellers of Australia (NIDMA)

- objectives
 - help build a mutually supportive research environment for the team,
 - create a closely connected team that will attract other researchers with related interests, and
 - provide a recognised resource for policy makers.

Timelines, governance

- 5 years, commencing June 1, 2005
- Management committee (internal)
- Steering group (external/internal)

Universitas 21

- U21 objective to identify a small number of collaborative research opportunities that would enhance the U21 consortium and build funding opportunities for research of global significance.
- Researchers from seven U21 universities met at University of Virginia January 2005:
 - Universities of Virginia, Nottingham, Hong Kong, Auckland, Queensland, Melbourne and McGill.
 - Commonwealth Fund (Robin Osborne), US Centres for Disease Control (CDC) (Mike Sage).
- This group's recommendation of '*biopreparedness*' was subsequently selected by the U21 Provosts/Deputy Vice-Chancellors (Research) to go forward.

Mathematical modelling for bio-preparedness

- Emerging infections and bio-terrorism
- Predict health, social, economic, other consequences
- Model optimal control and response strategies
- *Potential funding:* US Government (Centres for Disease Control)

U21 Objective

- To develop a consortium of parties interested in goal-directed mathematical modelling that will provide guidance for interventions for control of infectious diseases including those that might potentially result from bioterrorist activity, assessment of possible interventions, and testing of models in populations or in settings of outbreaks.

Research directions

- Assessment of social, psychological, and operational consequences of strategies for control of different infectious diseases in different societies e.g. acceptability of "quarantine".
- Acceptance of nursing responsibilities and preparedness e.g. nursing population behaviour in response to smallpox threat or request to be vaccinated as part of emergency response team.
- Interest in quarantine and laws relating to it. This would allow comparative studies, assessment of necessary interventions, and analysis of the legal and legislative responses
- Development of, and incorporation of, early warning systems for system perturbation (as is common in industry)
- Diseases of interest include SARS, avian influenza, HIV, hepatitis, emergence of microbial resistance, hospital acquired infections, lessons from Foot and Mouth Disease (UK).

Benefits

- This project would develop leadership, scientific importance and service.
- Include components not usually incorporated into models that relate to disruption of markets, network theory, influences on internationally assigned and local employees, and disturbance of government and civil society.
- Excellent opportunities for highlighting use of University or corporate data for disease alarm systems, research networks for prevention and treatment, practical model validation, early warning systems for system perturbation as used in industry