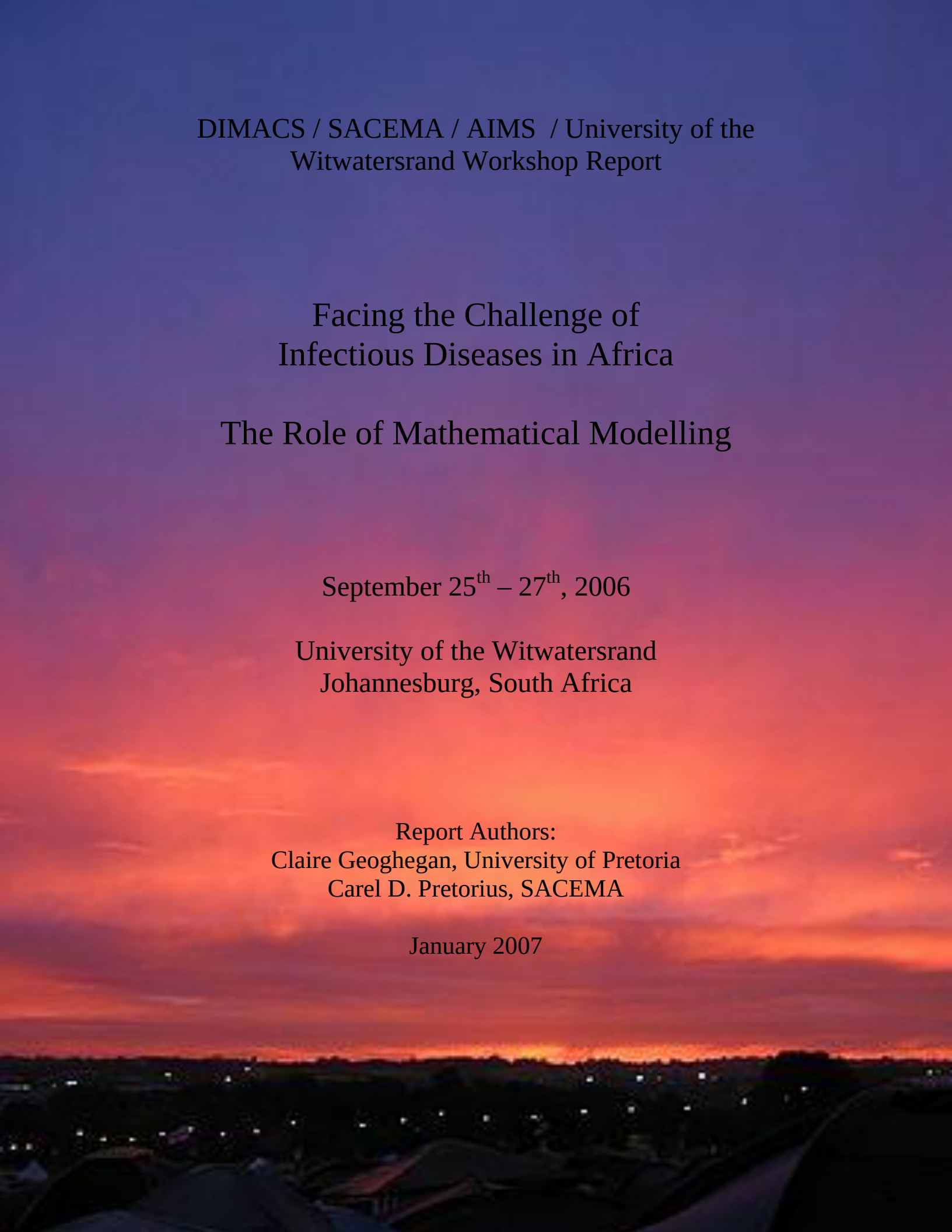

DIMACS / SACEMA / AIMS / University of the Witwatersrand Workshop Report

Facing the Challenge of Infectious Diseases in Africa

The Role of Mathematical Modelling

September 25th – 27th, 2006

University of the Witwatersrand
Johannesburg, South Africa

Report Authors:
Claire Geoghegan, University of Pretoria
Carel D. Pretorius, SACEMA

January 2007

Contents

Introduction ……..... 5

Current State of Infectious Diseases in Africa and Special Challenges for Mathematical Modelling

Problems in African Epidemiology: How Can SACEMA Help?
John Hargrove, DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA) ...……..... 7

Conjoined Epidemics: a New Problem for Southern Africa
John C.A. Davies, School of Public Health, University of the Witwatersrand ... 8

Overview of the State of Infectious Diseases in South Africa
Diana Dickinson, Physician and Director of Medical Services, Botswana 9

Modelling Transmission Dynamics of HIV/AIDS and Co-Infection with Other Diseases: Some Results, Issues, and Challenges
Abba Gumel, University of Manitoba ……. 12

So Much to Model, So Little Time (Current Examples of Epidemiological and Physiological Research in South Africa)
Alex Welte, University of the Witwatersrand ……...……..…. 12

New Challenges for Modellers (and Role of Discrete Mathematics and DIMACS)
Fred Roberts, DIMACS ……...……..... 13

Mathematical Modelling of Diseases that Inflict a Significant Burden on Africa: HIV/AIDS

Effects of Vertical Transmission on the Spread of HIV/AIDS in the Presence of Treatment
Edward Lungu, University of Botswana ……...……. 16

The Potential Role of HPV Infection in Vertical HIV Transmission
David Hill, Stanford University ……...…….. 17

Maternal Herpes Simplex Virus Type 2 Infection and Risk of Intra-Partum Transmission of HIV: Results of a Nested Case Control Study
Frances M Cowan, Royal Free and University College Medical School, University College London ……...……. 18

HIV-RNA Sequence Prediction: A Lattice Walk Approach to Modelling Sequences of the HIV-1 RNA Structure
Asamoah Nkwanta, Morgan State University …… 20

The Role of Mathematical Modelling in Epidemiology with Particular Reference to HIV/AIDS
Senelani Dorothy Hove-Musekwa, National University of Science and Technology, Zimbabwe ……..……. 21

Mathematical Modelling of Diseases that Inflict a Significant Burden on Africa: Other Diseases

Evaluating the Potential Burden of Zoonotic Mycobactria in Africa: Can Modelling Disease in Wildlife Populations Help?
Claire Geoghegan, University of Pretoria and Wayne Getz, UC Berkeley …… 22

Spatial Coherence and the Association of Temperature, Rainfall with the Incidence of Dengue Hemorrhagic Fever
Derek Cummings, Johns Hopkins Bloomberg School of Public Health and Donald Burke, University of Pittsburgh ……..…….…..... 24

Clonality in *Plasmodium Falciparum* Malaria
Ousmane Koita, University of Bamako, Mali …….……... 25

Epidemics in Strongly Fluctuating Populations
Aziz Yakabu, Howard University …….……... 26

Evaluating the Predictive Power of R0 in Wildlife Populations: Duelling Timescales of Host Movement and Disease Dynamics
Philip Johnson and Wayne Getz, UC Berkeley ..……..…….. 26

Modelling Issues Arising from the Threat of Emerging Diseases in Resource-Poor Countries: Pandemic Flu

SARS Outbreaks in Toronto, Hong Kong and Singapore: The Role of Diagnosis and Isolation as a Control Mechanism
Gerardo Chowell-Puente, Los Alamos National Laboratory ……..…..…... 28

Assessing Transmission Control Measures, Antivirals and Vaccine in Curtailing Pandemic Influenza: Scenarios for the US, UK, and South Africa
Miriam Nuno, Harvard School of Public Health ……..... 29

Vaccination Strategies

Estimating the Benefit of a HIV-1 Vaccine that Reduces Viral Load Set Point
Swati B Gupta, Merck Research Laboratories ……... 30

A Cost Effective Analysis of Alternative HPV Vaccination Strategies
Elamin Elbasha, Merck Research Laboratories ……..... 31

Models of New Vaccines for Measles
Derek Cummings, Johns Hopkins Bloomberg School of Public Health....…..... 32

A Model in Which Successive Infections With or Vaccinations Against Rotavirus Increase Immunity, Progressively Mitigating Symptoms
John Glasser, CDC ……..... 33

Optimization of Scarce Public Health Resources

Insights from Economic Epidemiology
Ramanan Laxminarayan, Resources for the Future ……..…… 34

Optimize What? Issues in Optimizing Public Health Resources through Mathematical Modelling
Michael Washington, CDC ……. 35

Preparing Social Infrastructure Against Disease-Related Workforce Depletion
Nina Fefferman, DIMACS and Tufts University ……..... 36

Summary ……..... 38

Acknowledgements …… 39

Introduction

Endemic and emerging diseases in Africa provide new and complex challenges for mathematical modelling. The DIMACS Workshop on Facing the Challenges of Infectious Diseases in Africa brought together scientists and public health practitioners, as well as junior researchers and students, from the USA and various African countries.

The 3-day workshop provided an opportunity for the 58 participants to share current understanding of disease modelling, and discover new perspectives that may help to combat the spread of emerging and re-emerging diseases. Participants were provided with the opportunity to forward an agenda for future workshops and encouraged to develop collaborations aimed at addressing the severe public health and socio-economic burdens inflicted by disease in Africa. By facilitating dialogue between scientists from developed and developing countries, each group was directly exposed to the real-world differences between facing diseases in resource-rich and resource-poor societies. Africa's unique environments, cultures, politics, religions, stigmas, and ethics must be factored in to public health initiatives if they are to be successful. Similarly, modellers must include knowledge of these differences in order to understand and overcome the difficulties associated with data acquisition, data sharing, model development, policy recommendation and practical implementation in a wide range of health scenarios. Most importantly, the workshop provided an opportunity for African scientists to interact and share information. This is an achievement that should not be overlooked or underestimated, as scientists across Africa often work in isolation, with few institutions providing the facilities required to develop inter and intra-continental collaborations.

The public health community is increasingly reaching out to mathematical modellers to provide much needed assistance in disease programme design. Modellers are now considered important allies in formulating strategies to manage a range of infectious diseases, including: HIV and HIV co-infections, tuberculosis, malaria, sexually transmitted infections, human papilloma virus, cervical cancer, pneumococcus, hepatitis B, dengue hemorrhagic fever, and a variety of animal diseases. Epidemiological modelling can make a substantial contribution towards understanding the disease transmission dynamics, recommending suitable forms of data acquisition and interpretation, and formulating public health policies and practice. These activities require careful operations research and optimization for successful delivery, especially in resource challenged settings, and so remain top priorities for providing better health care.

An example whereby mathematical models have been used to aid policy change is in Botswana. Here, policy makers were confronted with mathematic evidence that no developing country could afford to ignore the economic and social impacts of HIV. As a result, Botswana was the first country in southern Africa to initiate a commitment to

effective education, testing and treatment. This resulted in more than 80% of those HIV patients needing treatment receiving ARV therapy. This highlights the potential for modelling to effect real-world disease management. However, in order to maximize this influence, modellers have to package and market a diverse range of mathematical ideas into a public health toolkit; a process that was discussed and advanced via this workshop.

Mathematical tools to be applied include: i) Compartmental Modelling, a generalized differential equations approach used to model disease dynamics and control, ii) Network Models, a methodology believed to be a natural way of modelling the impact of heterogeneity and mixing, where applications include sexual networks in the spread of STIs, iii) Branching Theory, a powerful technique for modelling disease transmission dynamics, iv) Random Walks, where applications include the discovery of secondary DNA structures (encoding information for functionality of viruses, for example), by studying random walks on appropriately defined graphs, v) Agent Based Models, which attempt to simulate diseases mechanistically, giving a handle on the stochasticity of underlying processes, and vi) Optimal Control Theory, allowing resource management to be optimized with respect to suitably defined objective functions.

The following report should be viewed as a summary of the presentations given over the duration of the workshop. The report is divided into a number of sections, representing the topic sessions held over three days. These include: discussions on the current state of infectious disease in Africa and the subsequent special challenges for mathematical modelling; the role of mathematical modelling of diseases that inflict a significant burden on Africa, specifically HIV / AIDS and other diseases; the optimization of scarce public health resources; modelling issues arising from the threat of emerging diseases in resource-poor countries, including pandemic flu and vaccination strategies.

This report represents only one aspect of the workshop programme and should be considered in combination with the parallel reports from the workshop discussion groups, panel discussions and poster sessions in order to obtain a truly representative impression of the full range of activities that took place over the duration of the meeting.

Current State of Infectious Diseases in Africa and Special Challenges for Mathematical Modelling

Problems in African epidemiology: How can SACEMA help?

John Hargrove, *DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), South Africa*

Professor Hargrove introduced the newly formed South African Centre for Epidemiological Modelling and Analysis (SACEMA), an institution with a mandate to promote epidemiological modelling and analysis in South Africa. SACEMA is housed at the University of Stellenbosch in the Western Cape.

Understanding and controlling epidemiological processes requires development of innovative mathematical models and modelling techniques, and thus a reasonably high level of mathematical expertise. South Africa, like many other developing countries, is relatively weak in this technical area. SACEMA aims to: 1) complete work in the field of mathematical epidemiology that contributes substantially to the alleviation of the effects of major diseases and 2) strengthen sustainable capacity in South Africa by facilitating and funding: a) research by international and local scientists, b) training opportunities for young mathematicians interested in this field, c) visiting fellows to contribute to research and capacity building initiatives, and d) workshops and summer schools to collect small numbers of interested, talented individuals to focus intensively on a given modelling problem. Of particular emphasis will be the development of African scientists and students.

SACEMA will initially focus on researching HIV-AIDS and TB related diseases, with future expansion into areas that include malaria / trypanosomiasis, bovine TB, avian influenza, and other diseases. Projects currently receiving funding from SACEMA include: 1) a male circumcision project in Orange Farm, Gauteng where findings show a substantial decrease (60%), in transmission of HIV from female to circumcised males, 2) promoting the use of male circumcision as a public health policy for a general HIV epidemic, 3) HIV superspreading and the effect of individual variation on disease emergence, 4) in-vivo modelling of HIV infection, 4) HIV strain dynamics, and 5) suggested ways of adjusting current techniques for estimating HIV incidence from cross-sectional survey data. Substantial resources have been directed towards a collaboration with clinicians from two groups at the Desmond Tutu TB centre in the Western Cape (Woods/Lawn, UCT Medical School and Nulda Beyers, Tygerberg) to model and understand their unique data sets for a dual HIV and TB epidemic.

There are fundamental problems in the modelling of HIV epidemics that on occasion lead to major agencies, responsible for advising African governments, arriving

at inappropriate conclusions about trends in the epidemic. Professor Hargrove discussed the uncertainties associated with reports of HIV prevalence in the greater Harare region. Research conducted by the CDC suggested no change in HIV prevalence after about 1994/1996. This is in contrast with recent findings that suggest that HIV prevalence has been declining since at least 1998, and incidence perhaps as early as 1994. This discrepancy can be blamed on inadequate data, as well on incomplete models. SACEMA will (as much as possible) play an active role in data acquisition, processing and secure storage, in an attempt to ensure access to good data for SACEMA projects, and for a wider modelling community.

Conjoined epidemics: a new problem for southern Africa

John C. A. Davies, *School of Public Health, University of the Witwatersrand, South Africa*

In this talk Mr. Davies shared his vast experience in the public health sector of southern Africa, focusing on his experience with tuberculosis control in Zimbabwe. His talk encouraged much discussion and highlighted many issues that modellers will face when working on problems in this region. This is due to Africa's unique environments, cultures, politics, religions, stigmas, ethics, and so on.

Mr. Davies reported that there have been several oppressive developments in public health. The obsessive pursuit of treating established disease consumes almost all the available resources. A highly centralized bureaucracy effectively restricts freedom of action, rural health professionals work without support and politicians and human rights lawyers have usurped a public health function.

The countries of southern Africa face an unprecedented public health debacle. Control of the conjoined epidemics of tuberculosis and HIV/AIDS requires a complete break with the past and, in particular with the emotional and political baggage accumulated around HIV and tuberculosis in South Africa in the past decade. The following questions were discussed: 1) what is driving the epidemic of tuberculosis? and 2) what do we need to do in order not to fall into the trap of doing more of the same and failing again?

Discussions focussed on the risk groups of the dual epidemic. Although the risk group in a general epidemic is much smaller than the non-risk group for most diseases (plague, smallpox, measles), this is not the case for TB in South Africa, where the large number of salica exposed mine workers may be part of the reason for failing to control TB in South Africa.

Recommendations for southern Africa were discussed, including the fundamental principles of developing a strong partnership between epidemiological modelling and the application of public health strategies, following analyses of Zimbabwe's policies. Public

health interventions need to be evaluated against a properly constructed mathematical model, which will tell us exactly where we are going in controlling disease, and how fast.

Overview of the state of infectious diseases in South Africa

Diana Dickinson, *Physician and Director of Medical Services, Botswana*

This talk presented a clinical overview of the state of infectious disease in southern Africa from a Bostwanan medical doctor's perspective. It emphasised the problems, challenges, and social costs of disease in a developing world scenario, along with some new initiatives. Recommendations for modellers were given with reference to planning, changing policy and evaluating disease, with specifics for a number of diseases, including HIV, tuberculosis, pneumococcus, malaria, hepatitis B, herpes, cervical cancer and Karposi sarcoma.

HIV / AIDS: Approximately 40 million people were living with HIV in 2005 (2.3 million children), with 4.1 million new infections and 2.8 million deaths recorded in the same year. Over one-third of these deaths were in southern Africa, highlighting the potential impact of this disease in the region. Life expectancy has declined as a result, with figures predicted to be as low as 30 years for Swaziland by 2010, and less than 45 years for Botswana (<35), South Africa, Zambia (40) and Zimbabwe (38). Access to antiretroviral treatment in these areas varies from 75% coverage in Botswana, to less than 10% of those in need in Zimbabwe. Dr. Dickinson stated that the big change in Botswana's policy was aided by two reports that used models to predict the affects of the disease. Firstly, Brian Gazzard projected the reduction of medical and other costs for a nation when HIV is treated. Secondly, Jeffrey Sach projected a graph showing the lifetime risk of acquiring HIV as a 15-year-old boy in a number of African countries, which concluded that no developing country could afford not to treat HIV.

Tuberculosis: The global TB incidence continues to grow at 1% per year. In 2003, 9 million new cases of TB and 2 million deaths were reported, with the risk of TB infection at 5-15% per year in HIV positive patients, 50x the risk of those who are HIV negative. 30-40% of all HIV deaths in Africa are due to TB, as the risk of TB doubles in the first year of HIV infection. This affects a wide section of society, including the medical profession. In 1999 in Malawi, 2979 health workers died (50% had TB, 40% had AIDS) and 105 TB control officers. 80% of TB and HIV co-infected patients die in Malawi within 2 years of diagnosis, and 50% of those without HIV die within 7 years. 11-12% of TB notification are recurrences and relapse patients, which has a similarly close association with the HIV prevalence. Additionally, smear negative TB rates have increased in Malawi, which is a worrying trend as it is still infectious but is hard to diagnose and treat.

The use of Isoniazid Prophylaxis Therapy (IPT) reduces the risk of TB by 40% and recurrence by 50-80%. Highly Active Anti-Retroviral Therapy (HAART) reduces the TB risk but not back to regular levels. If a patient has no HAART, there is a risk of 9.7 cases of TB per 100 patient years, compared to 2.4 TB cases per 100 patient years in those on HAART. As 60% of TB deaths occur in the first 2 months, early HAART treatment reduces deaths. However, increased Immune Reconstitution Inflammatory Syndrome (IRIS) with possible death occurs as a result of early HAART in the first 3 months. Therefore, when deciding how best to treat a patient, a balance has to be obtained.

Pneumococcus: Acute respiratory infections are now the leading infectious cause of death in Africa. There is an increased prevalence of paediatric invasive serotypes in HIV+ patients, increased mortality, symptoms and signs. The degree of risk is also CD4 driven with counts being lower than usual. It traditionally affected the vulnerable age groups (young and elderly) but this has evened out throughout the population over the last five years. New risks have been seen including HIV+ status due to a lost immunity to the paediatric strains and antibiotic resistance due to illness, and if you are a young women, a health worker, have a small child in the home, or you abuse drugs or alcohol. Morbidity was reduced in Spain by giving HAART to HIV patients, where the rate of pneumococcal disease dropped from 24.1 to 2 per 1000 patients from 1985 to the present, but this has not been seen in southern Africa. Normal paediatric pneumococcal vaccines reduce the prevalence of paediatric serotypes and greatly reduce the risk of infection. However, other less virulent strains replace them so this is not completely effective in developing countries. It would therefore be useful to assess the relevance of vaccine use in areas of high HIV infection, which could be one future project for a modelling group.

Malaria: Along with HIV, malaria is the leading cause of morbidity and mortality in sub-Saharan Africa. Malaria is responsible for 500 million infections and 1 million deaths per year and has a wide geographical overlap with HIV. Clinical manifestations vary depending on the stability of the transmission areas. HIV aggravates the severity in adults and children, where there has been a 5% increase in mortality and a 1.7 fold increase in clinical disease in children under 5 years of age. The maximum impact has been seen in unstable transmission areas, where incidence has increased by 28% and deaths by 114%. Cotrimoxazol Prophylaxis has been used to achieve a 70% reduction of morbidity in Uganda, and a 97% efficacy to prevent infection in HIV negative children in Mali. Thus there are strategies to try and negate the impact of malaria that could be modelled, together with other factors to help provide governments with a way to tackle the disease.

Hepatitis B: HPV has a worldwide impact, with 2 billion infections, 400 million chronic infections, and 0.5-1.0 million deaths annually. It is acquired mainly between 6 months and 5 years of age through horizontal transmission via siblings. Some transmission is via sexual exposure and perinatal transmission. Co-infection with HIV may result in the reactivation of infection in silent chronic carriers, and new HBV infections as protective immunity is lost. However, in Botswana with a 40% incidence of

exposure, fewer than 1% test hepB sAG positive. The result is the IDCC no longer screen for this as numbers are so small that there is no impact on disease management.

Kaposi Sarcoma: This is more common among men in the west, but is more equally distributed in sub-Saharan Africa between genders. Incidence has risen in Zimbabwe from 2.3 and 0.3 / 100,000 in males and females prior to HIV infection, to 28 and 18 respectively in 2001. It has also risen in Uganda by 20 –30 times in the last 20 years, with 81% of patients being co-infected with HIV. Women seem to have a more aggressive and symptomatic disease, which may be due to cytokine and biological differences, although this is one area that requires more investigation and perhaps modelling of data.

Cervical Cancer: This is associated with oncogenic human Papilloma virus (HPV). It has increased in Africa across all age groups, which is a trend that was seen prior to and since HIV. Since the high infections levels of HIV, incidence of cervical cancer has risen by 1.88 with no change due to HAART observed. HIV+ women are more likely to be co-infected with HPV (58%) than HIV negative women (24%). They are also more likely to have multiple strains and to have a higher risk of infection (23% versus 14%). Aspects of cancer and HPV infection would be suitable for modelling, especially with regard to trends seen prior to and since the advent of HIV.

Genital Herpes: Herpes simplex 2 is responsible for recurrent outbreaks of genital herpes. It increases HIV shedding and the infectiousness of HIV+ patients, giving a higher likelihood of infection to exposed HIV negative patients. HIV also increased the severity and duration of lesions associated with the virus.

Other infectious diseases with differences in Africa include toxoplasmosis (which is common in the west but hardly seen in HIV patients in Africa), cytomegalovirus (higher exposure in Africa, 99,5% in Botswana compared to 50-65% in the west) and cryptococcus, which is very common in Africa. Diarrhoea in HIV+ patients may come from a range of bacteria, with recent outbreaks of cryptosporidium and enteropathogenic E. Coli in Botswana. These outbreaks are devastating, so work on the movement of bacteria within populations would be interesting from a modelling perspective.

In summary, medical practitioners need to influence policy and predict the changing faces of disease in light of HIV. They need to evaluate different prevention strategies and interventions, and to prioritise many aspects of public health care and service. Program planning requires information on many things, including the costs of prevention, testing, treatment, diagnostics and disease monitoring. Human resource managers need to calculate the number of health workers needed and the associated costs of employing and training more health workers.

Social care programs are also necessary, but are expensive. Evidence is therefore needed on how best to manage these different aspects of medical care. It is within these frameworks that modellers could be ultimately helpful, to paint fitness landscapes and

help assess the priorities for an ever expanding health service demand; something that over-worked and under-resourced doctors simply cannot do in the current situation.

Modelling transmission dynamics of HIV/AIDS: some results, issues and challenges

Abba Gumel, *University of Manitoba, Canada*

Since its emergence in the 1980s, the HIV/AIDS pandemic continue to pose an unprecedented threat to global health and human development. An estimated 34-46 million people are currently living with the virus, and over 20 million people have died due to AIDS-related causes over the last two decades. In addition to the enormous socio-economic burden it imposes, AIDS is now the leading cause of death in sub-Saharan Africa, and has cut the life expectancy in a number of countries in this region.

This talk addressed modelling issues and challenges associated with evaluating established and new strategies for curtailing the spread of HIV in resource-poor nations. Current strategies include the use of: 1) antiretroviral therapy, contrasting universal and targeted implementation strategies, 2) a potential (imperfect) vaccine, 3) condom use, and 4) male circumcision (MC). Another issue crucially important to modelling HIV spread in Africa is its interaction with other curable pathogens (opportunistic infections) such as mycobacterium tuberculosis and malaria. The key question here is how limited public health resources should be distributed between managing curable opportunistic infections and controlling HIV, and how an optimal result may be achieved when optimizing with respect to 'burden of disease' measures.

A discussion about MC campaigns highlighted the responsibility that programs have in assuring that reduced risk in acquisition of HIV after successful MC should not lead to a false sense of protection resulting in an overall increase in risky behaviour. The high degree of fatalities and other adverse side effects of traditional MC procedures highlights the responsibilities of programs to provide MC procedures by trained medical personnel along with appropriate post-surgical follow-up.

So much to model, so little time; facing the challenge of infectious disease in Africa

Alex Welte, *Computational and Applied Mathematics, The University of the Witwatersrand, South Africa*

The purpose of this talk was to stimulate discussion on the prospects and opportunities for disease related modelling in the context of current epidemiological research in South Africa, especially with regard to the HIV/AIDS problem.

Dr. Welte outlined a number of recent modelling applications that have been used in the local context, ranging from low-level laboratory data analysis to epidemiological inferences. One example was a project that reviews population dynamic type models of viral infection. A Bayesian framework was used to facilitate the inference of model parameters from clinical data from a recent trial. It appears that the rapid emergence of resistance is a challenge to popular unstructured models of viral infection. In particular, it appears that minimal ordinary differential equations, with their implicit exponential lifetime (constant hazard) distributions in all compartments, lack the short transient timescales observed clinically. This challenge is partly addressed by introducing some new models to describe strain competition and the infected cell lifecycle.

A second project involved the estimation of HIV incidence, a very current and controversial issue. Observing incidence directly requires a statistically significant and representative cohort, observed over a long period of time. The most widely used technique for estimating incidence indirectly, is to estimate the so called 'window period' as the varying amount of time individuals spend between detectable thresholds when analyzing assays from patients following HIV infection. This project develops systematic methods for estimating HIV incidence from 'recent infection', using cohort follow-up data from an acute HIV infection cohort. The mean duration of the window period (3-13 days, 95% Confidence Interval) was inferred in a shape independent way. The incidence (5-11 % per annum, 95% CI) and the prevalence of the window period state (0.06%-0.34%, 95% CI), was also inferred from the same data set, noting the consistency between these three inferred parameters.

Dr. Welte is involved in a number of projects, including: i) determining incidence from prevalence surveys, ii) inferring 'window period' duration, iii) acute infection cell/virus dynamics, iv) pooling samples for diagnostics, v) incidence from prevalence time series, vi) transiently detectable virus genotypes, vii) calibrating RT-PCR inferred relative gene frequencies, viii) viable cell/virion life cycle models, ix) dosing regimen impacts on virus ecology, x) immune system dynamics, xi) calibrating RT-PCR melt curves and xii) data mining sequencer chromatograms.

This diversity of mathematical applications, the relatively late stage at which modelling was introduced into these projects, and the small/transient group of modellers who have been involved, raises some tough questions about planning, prioritizing and managing research of this nature.

New challenges for modellers of infectious diseases of Africa, with emphasis on the role of discrete mathematics and the DIMACS initiatives

Fred Roberts, *Centre for Discrete Mathematics and Theoretical Computer Science (DIMACS), Rutgers University, Piscataway, NJ, USA*

This presentation discussed the background for the meeting and provided an introduction to the past goals and potential future roles of DIMACS. It described the main themes of the meeting, including the special modelling challenges arising from African diseases and the issues raised by emerging diseases in resource-poor countries. DIMACS aims to bring together USA and African researchers and students to collaborate in addressing the problems of public health and disease with regard to epidemiological modelling. Workshops, tutorials, working groups and exchange programs will help to facilitate these aims, as has been shown over the previous five years.

Mathematical modelling has been used to model the spread of infectious disease since Bernoulli, who modelled smallpox in 1760. Today's endemic and emerging diseases provide a new and complex challenge for mathematical modelling, especially in developing countries. Modelling can also play an important role in shaping public health policy decision as can be seen in developed nations like the UK, USA, Netherlands and Canada. It can provide insights leading to 'optimal' treatment strategies, and vaccine design and use with respect to adequate threshold coverage. During the SARS outbreaks in 2003, modellers and public health officials worked together to devise effective control strategies in a number of countries. This illustrates the new methods and approaches that are needed to deal with the large size and complexity of modern epidemiological problems. These include addressing the dynamics of multiple interacting strains of viruses through the construction and simulation of dynamic models; studying the spatial spread of disease through pattern analysis and simulation; and the early detection of emerging diseases or bio terrorist acts through rapidly responding surveillance systems.

In order to gain the maximum benefit from mathematical models they must be specialised: tested to ensure that the assumptions are correct in specific contexts and populations, with local data used to help define the key parameters. In addition, by encouraging scientists from developing countries to participate, access to data and relevant interpretation would be improved, yielding better and more realistic models. In return it would be important for non-Africa researchers to understand the effects of government policies in Africa on the current state of infectious diseases in Africa.

The focus of mathematical disease modelling has been on the most significant burdens. In HIV/AIDS, the evaluation of preventive and therapeutic strategies, the allocation of anti-retroviral drugs, the evolution and transmission of drug-resistant strains and the interaction with other infections like TB and malaria have been modelled. New methods of control and the impacts of climate and disease have been modelled with regard to malaria. The diseases of animals, specifically those with a zoonotic capacity, have been modelled, including bovine tuberculosis, avian influenza and trypanosomiasis.

Other aspects of disease specifically relevant to resource-poor countries include problems relating to slow communication, the short supply of vaccines and prophylactics, and the difficulty of imposing quarantines. Models have therefore been used to optimize scarce public health resources, allocate medicines, assign trained personnel to the most critical jobs, and design effective transportation and dispensing plans. Additionally,

computer simulations have been developed to compare vaccination strategies where field trials have been prohibitively expensive. It is one further aim that training programs for African and non-African students are developed to ensure the future of such work and initiatives.

Many mathematical tools have been used in epidemiological modelling, but the usefulness of newer tools of discrete mathematics and algorithmic methods of theoretical computer science have not yet been widely used in mathematical epidemiology. Statistical methods have been used to evaluate the role of chance and confounding associations, and to find sources of systematic error in observations. However, due to the increasingly large data sets involved, new approaches will be needed, which was a further point of discussion in this presentation.

Dynamical systems have been used for modelling host-pathogen systems and phase transitions when a disease becomes an epidemic. They use difference and differential equations but require powerful computational tools. Probabilistic methods use stochastic processes, random walk models, percolation theory and Markov chain Monte Carlo methods. Computational methods for simulating stochastic processes in complex spatial environments or on large networks have been used to simulate more complex biological interactions.

Discrete mathematics and theoretical computer science (TCS) methods have been used in many fields of science, and particularly in molecular biology. However, few have been used in epidemiology and mathematical epidemiology. When combined with geographic information systems (GIS), large and disparate computerized databases relevant to a disease can be combined via data mining techniques. TCS methods have also been used to construct phylogenetic trees based on evolutionary principles as they deal with arrangements, designs, codes, patterns, schedules and assignments. Unfortunately, these tools, which seem especially relevant to problems of epidemiology, are not well known to those working on public health problems.

One type of analysis based on these principles is cluster analysis, which extracts patterns from complex data. Traditional clustering algorithms are hindered by extreme heterogeneity of the data but newer methods need to be modified for infectious disease applications. Visualisation of the data can help, but algorithms become harder to develop when data is extracted from various sources. The data also often requires cleaning due to poor manual entry, lack of uniform standards, data duplication and measurement errors. TCS-based methods of data cleaning help remove duplicated records automatically.

The presentation offered some aspects of modelling disease transmission via the social network method. Contact information is often key in controlling an epidemic, and the use of discrete mathematical tools can help interpret these networks as graphs. Research issues include making use of other information about networks (e.g. semantic graphs), approximating parameters such as infectivity, susceptibility and latent periods that are not well specified, and making use of analogous lines of research such as the spread of opinions or education through social networks.

The discussion of models of evolution suggested that these may help shed light on new strains of infectious agents and new methods of phylogenetic tree reconstruction that may help identify the source of an infectious agent. Some relevant tools of discrete math and TCS might be disk-covering methods, nearest neighbour joining methods and hybrid methods.

One of the most important aspects of modelling infectious disease will be in aiding decision-making and policy analysis in under-resourced areas. Mathematical models can help with understanding fundamental processes, comparing alternative policies and interventions, providing a guide for scenario development, guiding risk assessment, and predicting future trends. Game theory, used in military decision-making, may be of use in allocating scarce resources to different components of a health program. Combinatorial group testing may be used when natural or human-induced epidemics require testing large populations. One example would be to identify all positive cases in a large population by dividing it into groups, testing if the group has at least one positive item and then iterating by dividing into smaller groups.

In conclusion, it is intended that this DIMACS meeting should be used to survey new methods and discuss new approaches for mathematical epidemiology, open up new lines of communication and lay the groundwork for future collaborations.

Mathematical Modelling of Diseases that Inflict a Significant Burden on Africa: HIV / AIDS

The effects of vertical transmission on the spread of HIV/AIDS in the presence of treatment

Edward Lungu, *University of Botswana, Botswana*

Dr. Lungu discussed a model designed to investigate if HIV drug resistant strains will cause high levels of transmitted HIV resistance and possibly lead to a reduction in the effectiveness of control efforts. This analysis is particularly relevant for treatment programs in Sub-Saharan Africa, a region affected by several barriers, including financial, organizational, physical and social.

The presentation further investigated if the increased transmission of drug-resistant strains will compound the current HIV/AIDS epidemic, as well the time scale within which this may take effect. This question is investigated by means of a model in

which the probability of transmission is varied along with characteristics of a treatment program in order to predict the spread of the disease.

The model is essentially a generalized SIR model, with a process by which susceptible individuals become infected. This is followed by disease progression through a sequence of strains or mutations (tuned in response to treatment), and also an orthogonal progression toward AIDS. This model allows different scenarios to be compared, by varying parameters that represent initial conditions (number of individuals infected with the wild-type and each resistant strain), as well as allowing all progression rates to be varied, and, importantly, the rate at which individuals seek treatment.

Different scenarios were compared where the initial population has equal prevalence of wild type and mutant strains. The rate at which individuals seek treatment was varied, together with the response to treatment (expressed as a fraction of those individuals developing resistance to treatment).

The model shows that the drug resistant population increases only slightly during treatment, when wild-type and resistant strains are transmitted with equal probability. A scenario where resistant strains increase their infectiousness (transmissibility) may have important implications for future control programs of HIV/AIDS in Sub-Saharan Africa, a region where adherence to treatment is generally accepted to be affected by low literacy and high poverty levels.

The potential role of human papilloma virus (HPV) infection in vertical HIV transmission: HPV co-infection in subtype C HIV-1-infected pregnant women in Zimbabwe.

David Hill, *Stanford University, USA*

This presentation focused on the role of human papilloma virus (HPV) in vertical HIV transmission in Zimbabwe. HPV is the world's most common sexually transmitted infection (STI), with roughly 80% of sexually active people infected at some point in life. Most HPV infection is transient, asymptomatic, and resolves without treatment. The significance of this disease is that persistent infection with high-risk types causes almost all (>99%) cases of cervical cancer. The high risk category include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82 and is associated with cervical cancer, while types 6, 11, 40, 42, 43 44, 54, 61, 72, 73, 81 are common types of the low risk category, associated with less severe conditions such as low grade cell changes and genital warts.

The association of HPV infection with the vertical transmission of HIV in southern Africa has not been explored. Dr. Hill is involved with a project to study the type distribution of HPV among pregnant woman with HIV infection, in a rural setting in Zimbabwe. This pilot study draws upon experience with other STIs and their role in facilitating vertical HIV transmission. The hypothesis that HPV in the genital tract will increase HIV shedding (and may facilitate HIV transmission to infants) is supported by

the knowledge that non-ulcerative STIs cause inflammation (and an increased local presence of immune/targeted cells), while ulcerative STIs provide portals of entry for the virus.

A clinical trial was conducted, enrolling 59 subjects from a cohort of HIV positive (subtype C) pregnant woman from a peri-urban high-density setting. Samples were evaluated for prevalence and type of HPV infection by assays of cervical swap samples. Polymerase chain reaction (PCR) was performed followed by a generic ("consensus") HPV probe using DNA hybridization. Consensus-probe positive samples were re-probed for 29 individual HPV types and a probe mixture of 10 types. Infant HIV-1 infection status was determined by ELISA at 12-18 months and PCR assays at birth and 2-weeks. PCR was performed, re-probing positive samples for 29 HPV subtypes and a probe mixture of 10 types. 77% of the samples were found to be HPV positive, with 25 HPV types identified in 34 women. The prevalence of high cancer risk types was as high as 58%. Six of the 43 infants acquired HIV infection, with HPV present in 83% of vertical transmissions.

With the generic probe, 77% (44/57) of the samples were HPV- positive. Re-probing identified 25 unique HPV types in 34 women, with a high cancer risk type prevalence of 58% (33/57). Individual types HPV 58 (16-like) and 59 (18-like) were the most prevalent, each found in 9 women, followed by HPV 61 and 66, each found in 8 women. Six of 43 (13%) infants acquired HIV infection. Among mothers whose infants were infected, HPV was present in 83% (5/6); among mothers of uninfected infants, HPV was present in 74% (32/43) (P = 0.58).

A high proportion of HIV-infected pregnant women in this population have cervical HPV infection. A broad diversity of HPV types is present, with a high prevalence of HPV types associated with increased risk of cervical cancer. This preliminary assessment of HPV carriage warrants further study of HPV types, HIV cervical shedding, and the association between HPV and MTCT of subtype C HIV-1.

Maternal Herpes Simplex Virus Type 2 infection and risk of intra-partum transmission of HIV: results of a nested case control study

Frances M. Cowan, *Centre for Sexual Health and HIV Research, Royal Free and University College Medical School, University College London, United Kingdom*

This talk focused on the Herpes simplex virus type 2 (HSV-2) and how it facilitates the sexual transmission of HIV. The possible effect of HSV-2 on intra-partum mother-to-child-transmission (MTCT) of HIV is unknown, and this talk reports on results from the Zvitambo study that answers some of these questions.

Variability in male circumcision and HSV-2 infection are considered to be the main reasons for substantial observed variability in HIV infection. This is a natural explanation for the variability in HIV infection for two studies based in West Africa

(Cotonou, *Nigeria* and Yaounde, *Cameroon*) and two in East Africa (Kisumu, *Uganda* and Ndola, *Zambia*), where sexual behaviour is similar among all groups.

Sexual acquisition of HIV-1 is likely to be increased by the presence of HSV-2 infection. Much less data is available to study the effect of HSV-2 on sexual transmission of HIV than on viral acquisition. Some of the known risk factors for transmission include: high viral load, more advanced HIV disease or primary disease and GUD (Genital Ulcer Disease). HSV-2 seropositivity per se is not associated with increased transmission risk. It is believed that HSV-2 effects the transmission of HIV-1 as it increases genital shedding of HIV from both clinical and sub-clinical HSV-2 lesions, and also (possibly) by increasing HIV-1 plasma viral load.

Intra-partum transmission of HIV is influenced by a number of factors, including maternal health, obstetric factors, and infant prematurity. A linear relationship exists between maternal plasma HIV-1 viral load and the risk of transmission. The role of STIs in intra-partum transmission is unclear, and presumptive treatment of bacterial STIs does not reduce the risk of intra-partum transmission. Clinical genital herpes during pregnancy is associated with increased transmission.

The Zvitambo study (conducted in Zimbabwe) is a randomised placebo controlled trial, aimed at discovering if giving Vitamin A to mothers and babies in the immediate post-partum period i) improved infant mortality, ii) reduced risk of mother to child transmission of HIV-1 through breast feeding, or iii) reduced the risk of women acquiring HIV-1 in the year after delivery. A case control study was performed using archived sera from Zvitambo, to see if: i) women with prevalent HSV-2 infection at delivery had an increased risk of intra-partum transmission of HIV-1, ii) women who acquired HSV-2 antibodies within 6 weeks of delivery had an increased risk of intra-partum transmission of HIV-1, and iii) women with serological evidence of active syphilis at delivery had an increased risk of intra-partum transmission.

Rates of prevalent and incident HSV-2 infection and syphilis were compared between 509 HIV-positive women who transmitted HIV to their infants during the intra-partum period and 1018 HIV-positive women whose infants remained HIV-uninfected at one year of age. Maternal sera collected less than 96 hours after delivery, and six-week samples from baseline HIV-negative women were tested for HSV-2 antibody. Six-week samples were also tested for syphilis using RPR and TPHA. TPHA positive women with RPR >1:8 were presumed to have active/incubating syphilis at delivery.

Prevalence of maternal HSV-2 at delivery was 82.5% (95%, CI 80.6-84.5) and 4.0% (95%, CI 3.0-5.1). HSV-2 incidence by 6 weeks was 17.3% (95%, CI 11.3-23.3). Prevalent HSV-2 infection was associated with increased intra-partum HIV transmission (adjusted odds ratio: 1.50 [95%, CI 1.09-2.08]). The proportion of intra-partum transmissions potentially attributable to prevalent HSV-2 infection was 28.4% (95%, CI 7.3-44.7). Women who became HSV-2 infected around the time of delivery also appeared to be at increased risk of intra-partum HIV transmission (adjusted OR 1.44 [95%, CI 0.57-3.69]).

Findings from this study were summarized as follows: HSV-2 infection is common among HIV-positive women and associated with an increased risk of intra-partum HIV MTCT. More than 25% of intra-partum HIV MTCT may be attributable to maternal HSV-2 co-infection. HSV-2 acquisition during the peri-partum period was common. Adding HSV-2 interventions to existing PMTCT programs might further reduce intra-partum transmission of HIV, although this strategy is unlikely to be worthwhile when using HAART.

HIV-RNA sequence prediction: A lattice walk approach to modelling sequences of the HIV-1 RNA structure

Asamoah Nkwanta, *Morgan State University, USA*

Understanding how biological sequences encode structural information remains a fundamental scientific challenge. This talk reported preliminary research on a random walk approach to predict (i.e. model or design) certain secondary RNA sequences, emphasizing the modelling of secondary RNA sequences that are essential for the expression of the SL2 and SL3 domains within the HIV-1 5' UTR RNA sequence. These domains are both hairpin structures that are important for HIV genomic packaging.

Given a primary sequence, the biological function of the related secondary structure was sought, which in turn is important for biological function. To achieve this goal the secondary structure was predicted (modelled). This talk outlines an algorithmic procedure that could achieve this goal, noting that the three dimensional shape (tertiary structure) is important for biological function, but it is harder to predict.

The central dogma of DNA transcription to RNA translation to protein production was explained. It was shown that RNA can be translated to DNA, and that RNA can also make copies of itself. It is still not possible to track from proteins back to RNA or DNA, and no known mechanism has yet been demonstrated for proteins that duplicate themselves. This discussion served as some general background to the molecular biology of the HIV virus, which belongs to a group of atypical viruses called retroviruses that maintain their genetic information in the form of RNA. Retroviruses are capable of producing DNA from RNA.

The secondary RNA structure can be conveniently mapped to a suitably defined graph, which refers in this context to set of n labelled points, where n is the length of the corresponding secondary sequence. This specification allows standard combinatorial and graph-theoretical tools and methods to be used to advance the understanding of secondary RNA structure. The speaker reported various relationships between classes of random walks that could be performed on these structure graphs, and showed that there is in fact a bijection between the set of RNA secondary structures of length n and the set of random walks of a certain class. This means that there is a one-to-one way of connecting classes of lattice walks (so-called Type I and Type II) to secondary RNA structure.

The overall goal of this ongoing project is to establish a direct link between certain subsets of random walks and secondary RNA sequences of the SL2 and SL3 domains, and to create a mathematical model that predicts more stable HIV-1 RNA sequences for further functional studies in HIV research.

The role of mathematical modelling in epidemiology, with particular reference to HIV/AIDS

Senelani Dorothy Hove-Musekwa, *National University of Science & Technology, Zimbabwe*

This presentation focused on some real-world implications of HIV/AIDS and highlighted the role of mathematical modelling in helping to provide decision makers with measures of intervention program success and predictions of future problems.

AIDS is a fatal disease for which the cause is known and the principal routes of transmission understood. As the prospects for curative therapy or effective vaccines are poor, governments, public-health agencies and health-care providers must determine how best to allocate scarce resources for HIV treatment and prevention. Control of the epidemic therefore depends on promoting behavioural change among the subgroups of populations where infection is taking place and on optimum use of available therapy for those infected.

By identifying HIV causal and preventive factors through systematic investigation of different populations and subgroups over time and space, these can be placed into a mathematical model to assist with disease programs development. Two fundamental assumptions were defined: human disease does not occur at random, human disease has causal and preventative factors that can be identified through systematic investigation of different populations over time and space. It is therefore important to understand the health problem, the characteristics of the disease, the demographics of vulnerable populations and the location and time factors associated with outbreaks, transmission and risk of infection. This is with a view that information and modelling outputs will be effective and lead to improvements in health status and care. It is therefore key that a model has explicit assumptions and testable predictions, a framework for data analysis, projections and various intervention possibilities, including outcomes, target setting, advocacy, and the possible combination of interventions.

Previous models were described to show that treatment of HIV-1 infection during the symptomatic phase has significantly improved patient survival. Furthermore, a two-strain HIV mathematical model that captures the dynamics of the immune system and two HIV-1 variants under antiretroviral therapy was presented. This explored the effects of

chemotherapy on the dynamics of two viral strains and T lymphocytes with one mutant strain phenotypically resistant to drug effects.

Model calculations show a common pattern for CD4+ T cell count increase during the first weeks of treatment. Thereafter the increase slows and is strictly by clonal expansion of pre-existing CD4+ T cells as plasma HIV RNA dramatically declines to zero levels during the first week of drug administration. The model shows that if drug efficacy is equal to or above a threshold efficacy, viral load remains at zero levels, or the viral load will gradually increase until it stabilizes. Viral rebound during treatment is therefore shown to be entirely due to the recovery of CD4+ T cells. The results also reveal that there is a dynamic equilibrium between viral load and cytotoxic T lymphocyte (CTL) response in an infected individual during drug administration.

Discussion concentrated on how data was used to validate the model, and the difficulties involved with understanding the interplay between variables that cause and affect infection. In this case, it is important to know how to evaluate the models, and it is particularly suggested that students are taught the wider aspects of mathematics and not just 'statistics'. Accordingly, teaching courses on the transmission dynamics of disease, and employing some mathematical content in the training of medical doctors and public health officials would be helpful. Collaboration between health workers, statisticians and mathematicians should also be intensified. Further questions included how treatment with interruptions or stopped treatment responded in the model. This had not been tested at this stage, although wild type elements had been shown to die.

Mathematical Modelling of Diseases that Inflict a Significant Burden on Africa: Other Diseases

Evaluating the potential burden of zoonotic *Mycobacteria* in Africa: can modelling disease in wildlife populations help?

Claire Geoghegan, *University of Pretoria, South Africa* and Wayne Getz, *UC Berkeley, USA*

This presentation focused on aspects of modelling zoonotic disease in wildlife populations, and how this may be used to assess similar diseases in humans, particularly tuberculosis. This was noted to be only one of the 62% of human pathogens that are attributed to animals.

Emerging infections are unique in the pathways they use to infect naïve hosts. They often have a drastic effect on host health and mortality due to the lack of co-evolution between pathogen and host. The pathogen can often infect multiple species and

become resident in the system, making it difficult to eradicate. Direct and indirect impacts of zoonotic disease can be seen in the economic and social environments, as well as on the conservation management of endangered species. Drivers of disease of particular relevance in Africa were noted to include changes of land use and agricultural practices, human demographics and climate change, poor population health, malnutrition, the quality of hospitals and public health programs, contamination of food and water sources, and the expansion of international travel and trade.

Annual incidence levels of *Mycobacterium tuberculosis* continues to rise, resulting in over one-third of the global human population contracting the disease. Over 95% of annual global TB cases are reported from developing countries, leading to over 3 million associated deaths. Combined with HIV co-infections, southern Africa faces one of the highest disease burdens. Consequently, tuberculosis eradication is considered to be one of the foremost public health priorities of the 21st century.

Bovine tuberculosis, (*M. bovis*, BTB) is a similar pathogen with an equally wide geographical distribution. It affects a wide range of wildlife and domestic animals, including threatened and economically valuable species, but appropriate data is unavailable for many developing nations. It is estimated to cause annual worldwide losses of over US $3 billion in trade alone. As BTB has the capacity to act as a zoonotic pathogen, human populations that are closely associated with infected animals face an increased risk of infection via aerosol and food born transmission.

Although the World Health Organisation first recognised BTB as a public health concern in 1950, very few studies have addressed the quantitative aspects of the disease burden in humans. Current data suggests that 80% of domestic cattle and humans in Africa reside in areas with no access to disease control programs. As levels of drug-resistant TB and HIV infections continue to rise, quantifying the role of BTB infection in human tuberculosis patients will be an important step in designing effective disease control programs. It was also noted that bovine tuberculosis is difficult to diagnose and treat due to the high resistance to front-line drugs. This extends the treatment period and requires the use of more toxic drugs, which has economic and social impacts on the patients – all aspects of the disease that may be incorporated into future models of zoonotic disease.

By analysing the spatial and temporal disease profiles of BTB in wildlife, livestock and human populations in rural communities, the study presented in this talk aimed to quantify the role of BTB as a zoonotic disease in South Africa. Results of the latest research on bovine tuberculosis in South African wildlife populations showed that by tracing individual movements of known infected and non-infected individuals, it is possible to predict the practical risk factors for infection and the potential for disease movement within known environments.

A unique approach to modelling disease in wild animal populations incorporated a network perspective, where the individual risk of infection depends on the number and frequency of connections with infected individuals in the population. This is a step away

from traditional animal disease models that assume random mixing of individuals and spatial disease models that assume limited dispersal between fixed groups.

Modelling these interactions has provided the opportunity to predict outbreaks and spatial and temporal aspects of disease dynamics that have been used for park management and disease control in Kruger National Park and elsewhere. Next steps will be to investigate links between this data and human health data surrounding the parks in order to develop an extended model for zoonotic transmission.

Discussion focused on how this work may continue in areas with little or no health facilities. Unfortunately this was recognised to be a fairly usual scenario for rural Africa and thus highlights the need to access reliable and longer-term data for use in models. The carrying capacity of species in protected areas, along with mapping disease in relation to landscape, water resources, and flooding events was discussed with a view to incorporating this level of information in future models.

Spatial coherence and the association of temperature, rainfall with the incidence of dengue hemorrhagic fever

Derek Cummings, *Johns Hopkins Bloomberg School of Public Health, USA* and Donald Burke, *University of Pittsburgh, USA*

This presentation described the use of a model to determine if seasonal variance in dengue hemorrhagic fever (DHF) in Thailand was associated with temperature and rainfall variance. Temperature was noted to affect the incubation period of the virus, survival rates, fecundity and biting rates of the mosquito vector. While rainfall affects were listed as affecting the survival and fecundity rates of the mosquito.

An empirical mode decomposition technique was used to examine the seasonal variance of DHF, rainfall and temperature in a large dataset describing monthly DHF incidence for 72 provinces between 1983-1996. This data was gathered by the Thai Ministry of Public Health and included roughly 850,000 cases. The mean monthly temperature and monthly rainfall information was obtained from 52 weather stations in 41 provinces over a period of 14 years by NOAA. This placed time-series data into modes of different periodicities. Using the non-parametric spline covariance function, temperature was shown to be synchronized across the country while DHF incidence and rainfall varied markedly in phase in different parts of the country.

Phase coherence analysis of DHF incidence and rainfall suggested that the timing of the dengue season is linked to the timing of rainfall across Thailand. Additionally, annual DHF incidence rates were also associated with higher mean annual temperatures. A two-stage hierarchical model was used to generate pooled estimates of the association between annual mean temperature, annual total rainfall and total annual DHF incidence across the country. The relationship was found to be modified by the distance from

Bangkok, with provinces close to Bangkok varying little with varying temperature, while those furthest away being more strongly associated with temperature.

This modification of the effect of temperature suggests that several processes at different temporal and spatial scales may be affecting incidence across the country. The association may be non-linear, with thresholds above or below which variation is less important. Seasonal processes may not be separable from underlying intrinsic dynamics. Next steps will be to examine some data at a finer scale and look at the correlation structure of each variable.

This presentation yielded discussion on data and how it is used. Participants agreed that the coarse scale of data (monthly) could prevent the model from showing subtleties that affect the disease distribution. It was suggested that seasons, rainfall and the breeding cycle of mosquitoes that harbour the disease should be factored in to future assessments. GIS could be used to explore spatial data. Local data on mosquito populations would be key to establishing phases of the disease. Unfortunately, data of the appropriate scale is not currently available since significant water can collect near human settlements in areas of garbage, old tires, etc. It was also noted that DHF was difficult to diagnose as not all children exhibit symptoms or shock. Four serotypes of DHF exist, so exposure helps increase childhood immunity and also has implications for type accumulation and disease cycling. It is estimated that most children have had DHF twice by the age of 15. This highlighted the need for further work on modelling predictions of DHF.

Clonality in *Plasmodium Falciparum* malaria

Ousmane Koita, *University of Bamako, Mali* and Donald J. Krogstad, *Tulane University, USA*

This presentation described the results of a study investigating the incidence of cerebral malaria due to Plasmodium falciparum, which is responsible for approximately 2 million deaths per year among children under 5 years of age. Meiosis, which takes place during passage through the mosquito, is a point in the life cycle with the potential for recombination between genetically different parasites.

Two groups of P. falciparum infected children were examined in Mali: asymptomatic children in the village of Bancoumana, and children hospitalized for cerebral malaria at the Hôpital Gabriel Touré in Bamako. Allotype-specific primers were used to amplify the variable (trimorphic: K1, MAD20, RO33) Block 2 region of merozoite surface protein 1 (MSP1) from parasite DNA in filter paper blots. Feeding experiments performed with gametocyte-positive subjects and laboratory-reared Anopheles *gambiae* mosquitoes were used to test for recombination between allotypes during passage through the mosquito vector.

It was found that parasites containing hybrid (MAD20 5'/RO33 3') sequences in Block 2 of MSP1 were more frequent among children with cerebral malaria than among asymptomatic infected controls (14 of 24 vs. 6 of 73, Odds Ratio = 15.63, $p << 0.001$). Among children with asymptomatic P. falciparum infections, parasite densities were greater with hybrid parasites (11,844 vs. 1,621 per µl, $p = 0.015$). Feeding experiments with gametocyte positive subjects demonstrated recombination between the MAD20 and RO33 allotypes within Block 2 of MSP1. They also revealed three differences between the sequences of most wild-type MAD20 parasites and the MAD20/RO33 hybrids consistent with changes in the sixth and ninth tripeptides of Block 2 from SVA/SVT and SVA/SGG.

These results suggest that parasites with hybrid MAD20/RO33 sequences are more virulent in part because they produce higher parasitemias, presumably because the hybrid Block 2 sequence alters the epitope(s) presented by MSP1. Because parasites with hybrid sequences in Block 2 of MSP1 are likely to have recombinant sequences at other loci in the genome, these results suggest that there may be other sites within the genome that are also risk factors for cerebral malaria. Finally, they provide evidence for recombination under field conditions in a variable (trimorphic) region of the parasite genome and suggest that recombination at the time of meiosis in the mosquito is an important mechanism for the expansion of genetic diversity in P. falciparum, which potentially enhances the ability of the parasite to adapt to drugs, vaccines and other interventions. This unique information may therefore be factored in to further analysis of P. falciparum, including models to assess potential treatment and prevention program success.

Epidemics in strongly fluctuating populations

Abdul-Aziz Yakubu, *Howard University, USA*

This presentation introduced an epidemic framework that includes both compensatory (contest competition) and over compensatory (scramble competition) population dynamics with and without the Allee effect. In this instance a mix of animals, humans and plants was used. The basic reproductive number, R_0, was computed and used to predict the (uniform) persistence or extinction of the infective population, where the population dynamics are compensatory and the Allee effect is either present or absent. The Beverton-Holt model was used for compensatory dynamics as fixed-point dynamics are supported. The Allee effect (named after W. C. Allee) describes a positive relation between population density and per capita growth rate of species. For example this could model the effect of humans on the control and amplification of disease dynamics on livestock as apposed to pure disease dynamics alone. The Ricker Model was also discussed as an example of over compensatory dynamics as it allows populations to oscillate.

The relationship between the demographic equation and the epidemic process was also explored, where the total population dynamics are over compensatory. It was shown

that the demographic dynamics drive both the susceptible and infective dynamics and as such, the framework is therefore suitable for studying diseases in animal populations, where even in constant environments, population cycles are not globally stable due to disease persistence, extinction, and the number of susceptible and infective individuals.

Evaluating the predictive power of R_0 in wildlife populations: duelling timescales of host movement and disease dynamics

Philip Johnson, Wayne Getz, Paul Cross and James Lloyd-Smith, *UC Berkeley, USA*

This presentation showed the difference between assessing infectious disease in wildlife / animal populations as opposed to human populations. The difference is due in part to smaller group sizes and limited intergroup movement. A principle question addressed was why a given disease may affect some species more than others. Potential answers include both immunological and behavioural differences.

The structure of a group falls into either phenomenological or mechanistic coupling, the former having most use when mixing of individuals takes place quickly. When placed within the context of a discrete 'susceptible – infected – recovered' (SIR) nonhomogenous Markov chain only one infected host is found in each group. However, when dealing with herds of individuals, as in wildlife populations, the force of infection, group size and movement patterns will all influence the spread of disease in a system.

It was explained that although the basic reproductive number, R_0, has traditionally been used to predict the probability of disease invasion, this application runs into trouble when used in highly structured wildlife populations. R_0 is interpreted as the expected number of new infections caused by a single index case in an infinite population where everyone is susceptible. However, it is often used with a threshold $R_0 > 1$ in finite populations with stochastic contact and a depleted susceptible pool as infection continues. Chronic diseases are more likely to invade than acute diseases with the same R_0 because the former persist in local groups long enough to allow host movement to spread the infection. A new predictive parameter, R*, takes into consideration the expected number of newly infected groups caused by a single infected group, rather than just an individual in the total population, again with infinite susceptible groups.

A discrete-time stochastic model with mechanistic host movement was presented to investigate these dynamics. After analyzing the predictive power of R_0 alone, classification tree analyses was applied (originally used for clinical risk assessment work). This was with a view to finding a superior combination of measurable variables that predict disease invasion and to minimise the misclassification rate of disease invasion via binary decision trees. R* was found to predict a pandemic better than R0 as it is probabilistic and not deterministic. However, newly infected and susceptible animals and animal populations are hard to estimate under any circumstances so there are still limitations to modelling disease in these conditions.

Questions included whether the simulations used in the research varied in size. The response was that it was non-spatial. Stepping stone and circle models were suggested as alternative approaches; specifically using circular models with spokes radiating out for further analysis.

Modelling Issues Arising from the Threat of Emerging Diseases in Resource-Poor Countries: Pandemic Flu

SARS outbreaks in Toronto, Hong Kong and Singapore: The role of diagnosis and isolation as a control mechanism

Gerardo Chowell - Puente, *Los Alamos National Laboratory, USA*

This presentation used a compartmental epidemic model to describe the transmission dynamics of Severe Acute Respiratory Syndrome (SARS) in Toronto, Hong Kong and Singapore. The model considers the effect of average infectiousness in a heterogeneous population to explore the role of patient isolation and diagnostic rate in controlling a SARS outbreak. SARS is a new respiratory disease believed to be transmitted by close contact with infectious individuals. The incubation period from infection to infectiousness is 2-7 days, leading to symptoms likened to pneumonia. Most infected individuals recover in 7-10 days, although mortality rates are higher for patients older than 60 years. These differences in the susceptibility of the population were accounted for in the compartmental model, using the parameters for the exposed, infectious, diagnosed, recovered and dead subgroups. The role of rapid diagnosis and effective isolation of infectious individuals in hospitals was evaluated. Rapid diagnosis was between 3 to 6 days with strict isolation procedures in place for all patients. This was found to decrease transmission by a factor of ten. Additionally, three hospitals in Toronto coordinated efforts to control SARS in order to prevent any one hospital facing a heavy burden from delayed outbreaks.

The mean number of secondary cases generated by a primary SARS case during its period of infectiousness (R) was estimated from time series data of the early epidemic phase. The model measured the transmissibility in a partially immune population where a fraction of individuals were effectively protected against infection before the start of the epidemic because of residual immunity from previous exposure to influenza or vaccination.

Data from other countries who have experienced influenza epidemics were used to test the model. The 1918 influenza pandemic in Geneva, Switzerland provides data that can be used to verify the 'spring' and 'full' wave in the current SARS outbreak. The reproduction number of the Spanish Flu pandemic is approximately twice that of seasonal flu, while the reproduction number of the first (herald) pandemic wave is in agreement with that of seasonal flu.

Discussion led to questions regarding the economics of vaccinating or quarantining patients, but as yet this hasn't been investigated in the model. It was also mentioned that having multiple waves of flu may be due to temperature fluctuations and sensitivity of the pathogen, and that this is not unusual but is hard to factor into prevention and model analysis.

Assessing transmission control measures, antivirals and vaccine in curtailing pandemic influenza: scenarios for the US, UK, and South Africa

Miriam Nuno, *Harvard School of Public Health, USA*

This presentation discussed the current urgency to develop pandemic preparedness plans worldwide for avian influenza. Leading recommendations to deal with the emergencies include using antivirals for treatment and prophylaxis, vaccination, and basic public health control measures for minimizing hospital (nosocomial) and community transmission (such as isolation, quarantine and social distancing). Flu preparedness plans of three countries, the USA, UK and South Africa, were presented for theoretical evaluation. The possibility of an 'optimal' flu pandemic preparedness was investigated by assessing the role of several interventions in reducing the burden of a potential flu pandemic. To this end, a compartmental modelling approach was used. This model allows hospital and community control measures, antivirals and vaccination in combating a potential flu pandemic.

Data from the USA indicted that hospital and community transmission control measures alone were highly effective in reducing the impact of a potential flu pandemic. The use of antivirals alone resulted in a reduction of the burden of the pandemic. However, the combination of transmission control measures, antivirals and vaccination remained the 'optimal' choice. However, such an optimal strategy may not be realistically attainable at the onset of a pandemic. Consequently, alternative (realistic) interventions need to be considered.

Using data from the USA, UK and South Africa, the 'optimal' preparedness plan was shown to be largely dependent on the availability of resources and should be considered country specific. For example, countries with limited resources should emphasize antiviral interventions therapeutically rather than prophylactically. However, countries with large antiviral supplies can achieve better reduction in disease burden by implementing them both prophylactically and therapeutically.

In addition, the importance of hospital and community transmission control measures in addition to the therapeutic (and timely) use of antivirals in reducing the burden of a potential flu pandemic was emphasized. A program based on the use of vaccination would have limited impact in comparison to those based on the use of antivirals or control measures for curtailing hospital and community transmission.

In summary, although the use of antivirals as prophylaxis seems promising, such a strategy entails the use of large stockpiles that may not be available or affordable in many nations in the world for economic and logistical reasons, particularly in resource-poor nations. This study was therefore important in identifying cost-effective alternatives. It was also shown that basic control measures reduce the burden of a pandemic, and that combined intervention is the most effective strategy in curtailing pandemic influenza.

Discussion raised questions on the use and incorporation of pneumococcal vaccines practically and in the model, and the inclusion of secondary infections. Concern was also expressed with regard to the ease of transmission in modern-day transport, especially on aircraft. The model could therefore be used to explore these areas in the future.

Vaccination Strategies

Estimating the benefit of a HIV-1 vaccine that reduces viral load set point

Swati B Gupta, Lisa P Jacobson, Joseph B Margolick, Charles R Rinaldo, John P Phair, Beth D Jamieson, Devon V Mehrotra, Michael N Robertson and Walter L Straus, *Merck Research Laboratories, USA*

This presentation focused on the use of models to assess the potential impact of HIV vaccines to reduce viral set point after infection. With 11,000 new HIV infections per day in 2005, and an increase in prevalence of 30 – 34% between 1990 – 2005 in African countries, vaccines are now seen as a critical aspect of disease control.

Vaccines designed to induce cell-mediated immune responses against HIV-1 are being developed but are likely to be associated with reduced viral set points after infection rather than providing sterilizing immunity. Current CMI-based vaccines may also be expected to prevent infection.

Using natural history data from 311 HIV-1 seroconverters, lognormal parametric regression models were used to estimate the log median time to events of interest. Relative times (RT) were estimated for those with viral load set points of 30,000 copies/mL (reference group) versus those with lower viral set points.

The time to key clinical events in the course of HIV-1 disease progression was significantly extended for those with viral set points 0.5-1.25 log10 copies/mL lower than the reference group. In reality, the time of events for HIV progression was halved. By quantifying the anticipated clinical benefits associated with a reduction in viral set point, these findings support the use of virologic endpoints in HIV-1 vaccine trials.

Discussion emphasised that this work was based on natural history data and only BHN-1, and did not include data on women. Similar analysis is needed on other cohorts before findings can be regarded as true in all cases. Questions raised included the usefulness of comparing viral load and transmissibility when it comes to public health and advising the individual. However, it has been seen in Ugandan studies that a reduction in viral load has led to a reduction in transmissibility. Other comments were that viral load isn't always thought to be connected with the time to AIDS conversion, but is predictive of the progression only. Other factors may be equally important and with so many HLA types it is difficult to analyse computationally, but it would be interesting to stratify the results by HLA types when possible. It was further noted that vaccine trials in Botswana had been abandoned due to the different types of HIV requiring different vaccines. It may therefore mean that clade specific vaccines will be needed for different areas, but this remains to be seen.

A cost-effectiveness analysis of alternative HPV vaccination strategies

Elamin H. Elbasha, *Merck Research Laboratories, USA*

This presentation assessed the cost-effectiveness of alternative Human Papilloma Virus (HPV) vaccination strategies in settings with established cervical cancer screening programs in the United States. More than 240,000 infection related deaths due to associated cancers occur in women per year. Protection is likely to be HPV type specific, but initial analysis has shown GARDASIL to be 100% effective against types 6, 11, 16 and 18.

A non-linear deterministic mathematical model of the transmission dynamics of HPV infection (types 6,11,16,18) and disease development in an age-structured population was developed and integrated with an economic model. Inputs for the model were obtained from public data sources, published literature, and clinical trials.

Compared with current practice, vaccinating females and males before the age of 12, augmented by a 12-24-year olds temporary catch-up program, was the most effective strategy, substantially reducing the incidence of genital warts, cervical intraepithelial neoplasia (CIN), and cervical cancer. Thus, vaccination with a quadrivalent HPV vaccine can provide survival benefits and quality of life improvements and is potentially cost-effective for a reasonably wide range of model input values.

Factors to consider in models of this type include the duration of protection afforded by the vaccine and how often the vaccine needs to be administered. Sensitivity

analysis is required to examine the costs of providing and administering the vaccine depending on the coverage required. If low coverage is preferred then vaccinating males would be most effective as they are the primary disease vectors, but analysis of the impact on related diseases and cross / multi-type infections would also be necessary.

Group discussion included the different coverage rates anticipated if targeting males and/ or females in a vaccination program. The model has been designed to allow modification for time, sexual behaviour, gender, infection type, etc. Concerns regarding the impact on screening practices and availability in light of vaccine use were expressed, but as it is not effective against all types of HPV, screening would still be required to control the virus.

It was suggested that the model should be adapted to look at vaccination from a funding rather than a healthcare perspective as few indirect costs are involved, and private health care functions on direct benefits so vaccination may not be an attractive option in South Africa. It was noted that this type of vaccine is already available in the private sector in the USA at a cost of $360 for five doses. This is too expensive for developing countries and it is likely to be 10 – 15 years before it becomes available there.

Models of new vaccines for measles

Derek Cummings, *Johns Hopkins Bloomberg School of Public Health, USA*

This presentation described an age-specific simulation model to describe the potential benefits of measles vaccines. Despite the availability of an effective vaccine, measles continues to cause a substantial amount of morbidity and mortality globally (more than 500,000 deaths per year) and especially in Africa. One strategy for reducing this burden is to develop new vaccines that can be delivered at younger ages.

The current vaccine does not induce effective immunity in children younger than nine months of age. A vaccine that could be given to younger children would reduce the reservoir of children who are not protected by waning maternal immunity and are not yet vaccinated. Such a vaccine would not only potentially reduce morbidity and mortality in this age group but also increase the probability of elimination of the disease altogether in some settings.

However, the specific benefit of these vaccines is not known even if they were available. A realistic age structure model and five disease states (indexed by age as force of infection and vaccines vary) was described. The age-specific force of infection was estimated from serological data in the UK and in Senegal. Age structure of the Cameroon population, informed by data from a 'Demographics and Health Survey', was imposed on the model. It was found that using more specific age classes made little difference in the outcome of the probability of disease elimination or reducing morbidity.

Discussion highlighted that population movement hinders vaccination campaigns. 'Entitlement' to vaccinations is also misleading and leads to a hidden strata of vulnerable or infected people. In the America's, vaccination has been given without prejudice but the success of eradication depends on the contact matrix of those who are infected with those who are not. Comments regarding the extension of health services highlighted that a number of factors can contribute to take-up, including cultural attitudes, religion and belief in alternative medicine. This dual system of healthcare needs to be factored in to disease models for real-world analysis. It was also suggested that an aerosol-administered vaccine would be safer in the long term but would require different models to assess in this manner.

A model in which successive infections with, or vaccinations against rotavirus increase immunity, progressively mitigating symptoms

John Glasser, Roger Glass, Umesh Parashar, Manish Patel, and Marc-Alain Widdowson, *CDC*

Rotavirus is the leading cause of severe diarrhoea among young children worldwide, with mortality greatest where oral rehydration therapy is relatively inaccessible. Children who survive their initial infections may be re-infected, but successive illnesses are milder as immunity develops. Rotavirus is so ubiquitous and replicates so rapidly that very few particles are required to infect naïve hosts. Preliminary calculations suggest R0 is higher than reported for any infectious disease. Even if the herd immunity threshold cannot be attained, vaccines that engender an immune response similar to a natural infection would mitigate morbidity.

Rotavirus transmission was modelled to better understand the epidemiology of severe diarrhoea due to rotavirus, and thereby assist in the design or evaluation, and possible improvement of programs for recently or soon-to-be licensed vaccines. The model uses a system of partial differential equations that describe transitions via infection and recovery among decreasingly susceptible (or increasingly immune) and infectious states, via vaccination among the same increasingly immune states, or combinations. Serotypes were not distinguished, but as one vaccine is mono- and other heterotypic, evidence of cross-protection would motivate this complication.

Characteristic epidemiological features of this disease (such as the younger mean age of first infections in tropical than temperate regions, due either to year-round versus seasonal risk or greater force of infection accompanying less sanitary environments) were incorporated where possible. This is with an aim to assist in the design of vaccination programs considering the younger mean age at first infection in the tropics. This may therefore mean that vaccination at two and four months of age might be optimal in the tropics instead of doses at birth, despite interference via passively acquired maternal antibodies. In temperate regions, schedules beginning at two months of age, when infant immune systems are more mature and interference is less likely, might be accelerated or

supplemented via mass campaigns prior to the rotavirus season. Where vaccination has begun, the impact (e.g., decreased environmental contamination in the tropics might increase seasonality via respiratory transmission) and suggest means of compensating was discussed.

It was suggested that analysis of natural and vaccination results should be compared for future use. The force of infection and the risk of susceptible infectees should be further investigated, together with the impact of rotavirus on adults in the same communities.

Optimisation of Scarce Public Health Resources

Insights from economic epidemiology

Ramanan Laxminarayan, *Resources for the Future, USA*

This presentation tackled an essential aspect of disease and epidemiology; how to conceptualise the interplay between economics, human behaviour and disease ecology to improve our understanding of the emergence, persistence and spread of infectious agents. It also considered ways to delineate the most optimal strategies and policies to control the spread of disease, i.e. how best to deploy scarce resources for disease control when epidemics occur in different but inter-connected regions, or when individuals adapt to the threat of infection by adopting protective measures.

Major points discussed included the individuals' response to disease (the decision to be vaccinated, treated or tested, physiological responses to drugs and resistance), as opposed to major government response (wait until a it is a public health problem or prevent infections initially.) These actions factor in to the public price subsidy argument. One example of this is: if those who choose to invest in a medical program get vaccinated this may in turn reduce the incentive for those outside the program to comply with regulations as they are at a decreased risk of exposure to disease since the majority of people are protected. Subsidies may also increase the number of people who will pay to be tested for a disease but this has no bearing on the behaviour of individuals after the knowledge of the test result and the potential for infectivity of other susceptible individuals. Additionally, monopolistic vaccine manufacturers may have little incentive to eradicate disease, as the market for their product would disappear with disease eradication.

Further, disease complementarities provide an incentive to invest in preventing one cause of death (for example HIV) only if you are sure you are not going to die from something else (TB). This can be translated into the need for regionally coordinated disease control for hospitals to offset the possibilities of outbreaks in areas close to those where a heavy investment in prevention has been made. On a regional scale, at low levels of infection in

different populations, it is preferential to treat the populations with a higher transmission coefficient because of the greater economic value associated with greater potential to prevent secondary infections. However, at high levels of regional infection, it is preferential to treat the populations with lower levels of infections since the higher probability of re-infection in high infection populations reduces the economic value of the treatment. It was also noted that a combination of quarantine with preferential treatment of a less infected region could bring explosive disease under control.

In summary, mathematical models that capture the complex interplay between economics, human behaviour, and disease ecology may be more helpful in understanding how diseases evolve and spread than models that rely on epidemiology alone.

Group discussion raised a number of points. Measuring secondary impacts of disease on societies is difficult and hard to quantify and include in models. A higher level of sophistication would be necessary for this to be feasible. It is equally difficult to factor in individual behaviours and cultural aspects to health service use. For example, the compulsory immunisation of children in Zimbabwe would not work in Rwanda, where laws and traditions are very different and no medicine that is left over may remain in the house. It is therefore important to consider local traditions when constructing models of behaviour and economics.

Optimize what? Issues in optimizing public health resources through mathematical modelling

Michael Washington and Martin Meltzer, *Department of Health and Human Services, Centres for Disease Control and Prevention (CDC), USA*

This presentation addressed the challenge of optimizing public health decisions, systems, and resources and the usefulness of mathematical modelling. Three concerns, namely, deciding on an objective (when there are many factors to optimize and different stakeholders have different priorities), identifying constraints and presenting results effectively were outlined. In short, results may be optimal for one segment of the population, but detrimental to others, presenting a significant challenge to public health officials.

Other constraints highlighted include the ability to create an accurate model of a disease and identify the constraints hidden within that model. Results are often purely mathematical and thus are hard to apply to the real world, although this also depends on the objective of the model and economics involved with the outcome.

Two examples were used to discuss these aspects. A decision tree model was used to analyze the cost-effectiveness of Lyme disease vaccinations. The model results showed that cost savings would occur if the vaccine was only targeted at individuals whose annual risk of contracting disease was greater than 3%. In addition the model illustrated

that an alternative technology, working to improve the likelihood of early detection and successful treatment was probably more cost-effective than vaccinating those with lower risk (e.g., 0.005/ year).

A second example used a discrete-event computer simulation model that allocated staff in a vaccination clinic, with the goal of maximizing numbers vaccinated per day. The results indicated that clinic staff should focus on the groups with the largest numbers (i.e., the general population), which meant that special groups, like the frail and elderly, spent more than twice the time in the clinic as the other groups. Although alternative objective functions could have limited this disparity, it would have made the clinic less efficient, and thus not able to vaccinate the maximum number of people. Interested readers are referred to www.vaccineselection.com and www.cdc.gov/flu/pandemic/preparednesstools.htm to explore software tools used in these two examples.

These examples clearly illustrated the power of mathematical modelling to clarify a potential set of options and the consequences of those options. However, it also showed that the results of mathematical optimization may run contrary to expectations. Discussion included how these models may be used on a regional level and whether it is wise to bring together many sections of society for widespread immunisation for fear of transmitting other diseases during that time. It is also clear that it is important to understand the inadequacies of the data being used to develop models, so that a 'one fits all' scenario is not seen as a final result.

Preparing societal infrastructure against disease-related workforce depletion

Nina Fefferman, *DIMACS and Tufts University, USA*

This presentation discussed preliminary models examining how to plan ahead when disease related work-force depletion causes the breakdown of necessary societal infrastructure, and threatens the safety of a population over and above the direct effects of serious illness. The question is asked if we can train or allocate our work force according to an algorithm in order to minimize such concerns.

The model considered a number of scenarios including redundancies in the training of a workforce, when to use a workforce deployment for critical positions, the cost of switching people to a new task, the minimum number of people for a certain task to continue functioning effectively, the rate of production required so that no detrimental effects are felt by society, direct and indirect mortalities, risk of exposure and seasonal variations in all the above. In addition to disease risk, an "additional risk of mortality" was included as a function of how many tasks have fewer than the minimum number of workers needed to accomplish them. This represents indirect harm caused by the breakdown in infrastructure support. Once defined, the model can simulate a population (which can be described as essentially antlike in their obedience regarding assigned tasks), with new workers being recruited into the system, and/or learning and progressing

through new tasks over time, according to a variety of different strategies. The following learning strategies were studied: i) permanently defined tasks, ii) tasks allocated by seniority, iii) repertoire increase with seniority, and iv) random task allocations.

Various simulations were performed, applying constant or periodically changing environments to a population subjected to the above-mentioned training and task allocation strategies. Results are expressed as work produced by a workforce performing an increasing list of tasks (i.e. the amount of work as a function of a task). It was found that introducing 'additional risk' assumptions does not have substantial influence on deterministic or random strategies (i and iv), but makes a huge difference on work yield under discrete and repertoire strategies (ii and iii).

It was discussed how more specific diseases, populations and infrastructures may be examined, amounting to appropriately tailored simulations. Final discussion was based on how such planning should change to reflect the threat posed by the disease itself (e.g. seasonal depletion from malaria, or constant growth from HIV / AIDS), the presence or absence of disease and differential risk.

Summary and Future Directions

This three-day event consisted of individual presentations and group discussions. It successfully brought together mathematical researchers, medical professionals, clinicians, ecologists, microbiologists, economists, laboratory scientists, pharmaceutical industry representatives, operations researchers, public health officers, students and members of both government and non-government organisations.

A deeper understanding regarding the needs for endemic and emerging disease control was achieved, especially with regard to the unique challenges faced by developing countries. It was also recognised that Africa is a continent that encompasses a range of cultures and environments. Consequently, models should be adapted for each individual environment based on the input of local scientists and stakeholders so that assumptions are not generalised across perceived boundaries. This intrinsically was felt to be paramount to enhancing the credibility and usability of any developed models, especially with regard to how they would be seen by a range of public health users. One step towards achieving this was taken by having this workshop, which integrated the perspectives of African regional scientists with those from developed western backgrounds.

Recommendations for the direction of future work and research were discussed, and included the following:

- Epidemiological modelling should maintain a wider focus to enable local factors to be included in model development. Examples may include regional drivers of disease like migration, co-morbidity, malnutrition and conflict. Additionally, capacity analysis should be encouraged, which, for example, may be essential for successful vaccine rollout.
- Measures of disease should incorporate the level of direct burden placed on a country, and not simply the monetary costs. This includes developing uncertainty analysis and optimisation strategies for parameters including salaries, drugs, infrastructure, facilities, etc.
- Simple guidelines for data collection, storage and the standardisation of measures (including medical, social, economic etc.) should be produced. This will help prevent the duplication of efforts required for data collection, ensure data is in a consistently useable form and prevent the loss of information, all problems experienced in disease management.

It was felt that the specific goals of this group should be to enhance the advancement of mathematical and epidemiological training for a range of interested stakeholders and to promote inter-disciplinary science. This may take a practical form of offering courses and workshops for professional and student development and also of

facilitating greater inter-disciplinary collaboration. This would help to establish greater communication between scientific groups and with local communities. This in turn would help to maintain a degree of momentum and continuity of thought over time. It is also hoped that greater collaboration between African scientists with those elsewhere will aid in the publication of results based on the work presented during the workshop. Finally, it was felt that the group should aim to support collaborative research and workshop attendance through the allocation of funding for scientists and students from resource-poor areas.

Overall, this workshop was considered to be a very successful event that facilitated the ongoing collaboration between US and African scientists. It is hoped that further meetings will continue this work and ultimately contribute towards the effective and applicable modelling of infectious disease in Africa.

Acknowledgements

DIMACS, the organizers and authors would like to acknowledge the support of the Burroughs-Welcome Fund, (grant number 1006051), and the National Science Foundation, (grant number OISE 0629714).

The workshop would like to thank the following sponsors: African Institute for Mathematical Sciences (AIMS), Burroughs Wellcome Fund, DIMACS, US National Science Foundation, South African Centre for Epidemiological Modelling and Analysis (SACEMA), School of Computational and Applied Mathematics, the University of the Witwatersrand, Witwatersrand AIDS Research Initiative.

We would like to thank all the speakers who have contributed to this report by sharing their abstracts and presentations. The authors would like to apologise to those whose work has not been fully and accurately described, which is merely a reflection of the limitation of the authors' knowledge and availability of materials, and has no bearing on the quality of the work. We therefore direct interested parties to contact the presenters directly for further explanation of their work when necessary.

The authors would also like to thank the organizing committee for the opportunity to contribute to this workshop through the preparation of this report.