



SACEMA
DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis

SACEMA NEWSLETTER
No 9: March 2008

NEWS:

NEW STAFF:



We would like to welcome our new postdoctoral research fellow, Dr Simon Childs. Simon received his PhD in Computational Fluid Dynamics from the I.F.T.R. Polish Academy of Sciences in 2003. While at SACEMA he will be working on developing a general model for the population dynamics of the trypanosomiasis and their vectors the tsetse flies, *Glossina* spp. More immediately he is developing, with John Hargrove, a general model for the expected outcome of aerial spraying campaigns against tsetse. Simon's work is part of SACEMA's collaboration with the Onderstepoort Veterinarian Institute, which was initiated last year.

MALE CIRCUMCISION VOTED NO. 1 MEDICAL BREAKTHROUGH OF 2007

The role of male circumcision in preventing the transmission of HIV was voted by Time magazine as the Number One medical breakthrough of 2007. For more information see the full article at: http://www.time.com/time/specials/2007/top10/article/0,30583,1686204_1686252_1690372,00.html SACEMA associate, Prof Bertran Auvert, was one of the pioneers of this work through his trial in Orange Farm in South Africa. SACEMA continues to provide support Prof Auvert's work on theoretical aspects of the projected roll-out of male circumcision in Africa.

CONFERENCES/WORKSHOPS ATTENDED BY STAFF:

Dr Rachid Ouifki attended an international conference on biomathematics hosted by Marrakech University from 3-8 January 2008. He presented a paper on the impact of delays on dynamical systems, titled: "Small delay induced oscillations in systems of differential equations with state dependent delay".

Prof J Hargrove was invited to present at a World Health Organisation Reference Group on Incidence Estimation, also in January. He gave a presentation on the latest results arising from BED analyses of samples provided by patients referred to Tygerberg hospital for antiretroviral therapy. Consequent on this, he was asked to head a sub-committee on optimising window estimation for the STARHS methods of estimating HIV incidence from cross-sectional surveys.

EVENTS:

SACEMA STRATEGIC MEETING, 25-26 February:

SACEMA staff and guests went away for two days to consider SACEMA's future research and institutional agenda for the next three years. We were pleased to have both Prof Brian Williams, Chair of the SACEMA Trust, as well as Prof Edward Lungu, Extraordinary Professor in the Mathematics Department, in attendance.

The major outcome was the identification of SACEMA's priority research area in HIV incidence estimation – significant work is already being done on this front by several of SACEMA's researchers, and it has the potential to be a research area that can be significant in assisting the SA Department of Health with the management of the HIV epidemic in this country.

Major research questions relating to various projects were discussed and the way forward planned for the initiation of several new projects. Staff further committed themselves to a goal number of publications to be written over the next few years.

SACEMA RESEARCH MEETING, 28-29 February:

SACEMA invited all our students, their supervisors, and various guests to a two-day meeting looking at all the research currently being funded through SACEMA. Staff presented on their own work, and students on their progress, or the new students on their proposals.

This was a good means of finding interactions and synergies between the various research projects and much discussion was held over the 2 days on maximising the collaboration potential between all SACEMA stakeholders.



*Students, staff and supervisors at the Research Meeting
(it was a very sunny day!)*

**UNAIDS/WHO/SACEMA Meeting:
Making Decisions on Male Circumcision for HIV Risk Reduction: refinement of Male
Circumcision Decision Makers' Tool
London, UK, 5-6 March 2008**



In March 2008 SACEMA co-hosted, with UNAIDS and the WHO, a third meeting on Male Circumcision. This meeting, held at Imperial College, London, was a follow-on from the meeting held at SACEMA in November last year.

The purpose of the meeting was to bring together a small working group of mathematical modellers to compare, develop and refine models for input into the male circumcision decision makers' tool that was discussed at the earlier meeting. An additional output of the meeting was the drawing up of a consensus statement on the potential impact of male circumcision on the transmission of HIV.

This consensus statement will be released at the next World AIDS Conference in Mexico, and has been submitted to the Lancet. Key points from this statement cover the cost-effectiveness of male circumcision as an HIV prevention technique, the potential population benefits, and the relative benefits to men and women.

The meeting was attended by researchers and modellers from UNAIDS, WHO, Imperial College, London School of Hygiene and Tropical Medicine, University of California San Francisco, Arab Emirates University, Statistical Centre for HIV Research and Prevention, INSERM, Centre for Actuarial Research UCT, Johns Hopkins University, and SACEMA.

RESEARCH UPDATE

The following are some selected highlights of research work done to date (and do not reflect the full extent of research conducted by SACEMA):

Incidence Estimation

With the identification of this area as a priority area for SACEMA's research, much work was done during 2007. The BED assay adjustment was fine-tuned significantly to provide much improved estimates on the ZVITAMBO data. This was achieved by adjusting for the proportion of people known to have been infected for long periods (more than a year) but who continue to test as recent infections by BED. Of importance was the fact that the required adjustment was almost identical for post partum women in Harare (HIV subtype C) as it was for male homosexuals from Holland and the US (HIV subtype B), showing that there is no reason this method could not be used to estimate HIV incidence accurately in Africa in the same way as has been done in the US.

HIV incidence estimates elsewhere in Africa, however, have again resulted in obvious overestimates, possibly reflecting major variation in the required adjustment with gender, geographical localities and HIV subtypes. Potential alternative sources of variation and error could be disease stage and time spent on antiretroviral therapy (ART), which was investigated by estimating the required adjustment from a sample of women and men with presumptive long-term infections referred to Tygerberg Hospital, Cape Town for ART. This showed that an unusually high proportion of false recent cases occurred among people with CD4 counts less than 50 and among those who were on ART. Excluding these cases from the analysis resulted in adjustment levels that did not differ significantly from those estimated from the ZVITAMBO data – although the sample sizes are still too small to allow accurate estimates of the adjustment for samples similar to those found at Tygerberg.

These results do, however, suggest the following:

- i) The adjustment required for South African BED assays may not differ greatly from that used in Harare.
- ii) The above being true, appropriate use of the BED method could provide a much better, cheaper and easier way of estimating HIV incidence in South Africa.
- iii) It will be necessary to identify as long-term infections those cases where the CD4 count is <50 and/or cases known to be on ART, which cases need to be removed prior to making an estimate of the required adjustment. The cases also need to be defined as long-term infections in cross-sectional survey samples prior to the estimation of the incidence.

Major efforts are planned for 2008 work using samples and data from South Africa.

In addition to this, a theoretical framework for the estimation of incidence by techniques such as the BED has been developed by T McWalter and A Welte. The work focuses on the fundamental aspects of making inferences about non-constant population dynamic processes by making observations at a point in time, with particular reference to assays which observe early disease progression with considerable inter-subject variability. The obvious application which this targets is the development of systematic methods for inferring HIV incidence from cross sectional surveys of 'recent infection prevalence'. A foundation has been laid with the formal analysis of a basic model which in principle can be calibrated. Extensions and benchmarking against competing formulations are natural next steps.

HIV Population Level Analysis

Analysis on the latest Zimbabwe ANC data has confirmed SACEMA's contention that HIV prevalence in that country has been declining rapidly over the last few years. A series of models has been developed, led by Prof Brian Williams, showing that this trend has been ongoing from the mid-1990s. The much more difficult task, of fitting the data for prevalence and incidence disaggregated on age was initiated by Prof Hargrove and is currently being led by Dr Travis Porco of the University of California, San Francisco.

Additional work on population level analysis was done by Dr Ouifki, looking at dynamics of HIV and TB and their interactions. Two papers were completed in this area, with models with periodic factors showing that apart from a few exceptional parameter values, the epidemic threshold depends not only on the mean contact rate, but also on the amplitude of fluctuations.

In addition, a mathematical model for the interaction between HIV and TB epidemics was developed using data from a township near Cape Town. Model parameters were estimated to study how various control measures might change the course of these epidemics. A presentation and paper resulted from this work:

N. Bacaër, R. Ouifki, C. Pretorius and R. Wood, "Modeling the joint epidemics of TB and HIV in a peri-urban community in South Africa: what are the prospects for control?" 38th Union World Conference on Lung Health, 8-2 November 2007. <http://www.worldlunghealth.org/Conf2007/website2/>

N. Bacaer, R. Ouifki, C. Pretorius, R. Wood and B. Williams "Modeling the joint epidemics of TB and HIV in a South African township" (submitted for publication to *Journal of Mathematical Biology*).

Tuberculosis: the effects of delays to diagnosis and reinfection

During 2007 Dr Pieter Uys, and Mr Stephen Millen, an MSc student from Southampton University, investigated the critical factors leading to delay in the diagnosis and treatment of tuberculosis in resource-poor settings.

The impact of each of the factors leading to delay was analysed and it was found that the sensitivity of the diagnostic method was the most significant factor. Thus, in a developing country, the low sensitivity of the initial sputum smear microscopy test potentially significantly increases the total diagnostic delay time experienced by TB patients. These results reinforce the urgent need for novel diagnostic methods that are highly sensitive and accessible at the point of care in order to reduce the associated delay to diagnosis.

In a separate study, Van Helden, Warren and Uys further considered the delay to diagnosis in TB. The existence of a threshold delay value was demonstrated where it was shown that unless a

sufficient number of cases are detected before this threshold, the epidemic will escalate. Intervention strategies to increase the threshold value relative to the time to diagnosis and which thereby decrease disease incidence became evident from a mathematical analysis of this threshold delay.

Another study between Van Helden, Warren and Uys considered the role of re-infection in the TB epidemic, where, in a significant number of instances, an episode of TB disease can be attributed to re-infection. It was also shown that the rate of re-infection of people who have recovered from a previous TB disease episode is higher than the rate of first-time infection. From a purely theoretical investigation it was shown that a simple relationship can be expected between incidence and the proportion of cases due to re-infection after a prior episode of TB. This relationship is approximately logarithmic and is sustained by a rate of re-infection that is higher than the rate of first-time infection. This latter consideration underscores the importance of monitoring recovered TB cases for repeat disease episodes, especially in regions where TB incidence is high.

Paediatric TB

Drs Ouifki and Nyabadza have made a start on modelling in this area. Large numbers of TB cases in the adult population lead to the spread of TB in children with their development of primary infection. When acquired during childhood, primary tuberculosis may develop into serious tuberculosis diseases within a short period of time or remain latent during childhood only to be reactivated in adulthood. Infected children represent a pool from which a large proportion of future cases of adult TB will arise.

Public health programs on TB prevention have excluded children. Lack of contagiousness is one of the reasons for that; children are regarded as posing no threat to other individuals. This work aims to challenge public health policies regarding childhood TB because of this reasoning.

Ouifki and Nyabadza developed a mathematical model that endeavours to capture the underlying factors that drive the epidemic in children. The intention is to look at the role of increased adult TB control on the growth of childhood TB and vice versa. They also intend to assess the proportion of adults that need to be targeted in order to control TB in children.

Modelling of the dynamics of mosquito populations

SACEMA Visiting Research Fellow Prof Glyn Vale, has been adapting and applying techniques he developed for the study of tsetse flies, for carrying out innovative experiments on mosquito behaviour in Zimbabwe. He continues with the development of a user-friendly model of the dynamics of mosquito populations and the diseases they transmit.

In modern research to combat mosquito-borne diseases, relatively little attention seems to be given to refining the methods of attacking the vectors, perhaps because the general feeling is that all avenues in this direction have been fully considered already. However, the experience with tsetse suggests that improved control might still be derived from a fuller and more quantitative analysis of the host-orientated behaviour of mosquitoes. To begin exploring this, field work with *Anopheles arabiensis* and other mosquitoes was performed at Rekomitjie Research Station, Zimbabwe, in association with the Natural Resources Institute, UK, and others in 2006. Some loose ends in the work were tidied up in 2007, under the auspices of SACEMA. In parallel with this, the development of the SacemaM model for the control of mosquito-borne disease has been adjusted to give fuller consideration of behaviour-based possibilities in mosquito control.

In addition, 2007 fieldwork with mosquitoes was done to confirm the 2006 work indicating that traps commonly used to study mosquito responses to hosts can give potentially misleading information, while also showing that carbon dioxide at release rates equivalent to the natural doses from humans and cattle was insufficient on its own to explain mosquito attraction from a distance, nor affect their entry responses into traps.

A paper reporting the results of the 2006 and 2007 work was accepted by *Medical and Veterinary Entomology* in 2007, and is expected to be published in April 2008.

SACEMA 2007 PUBLICATIONS

HIV and TB

1. Lungu E. Anti-tuberculosis resistance in patients co-infected with HIV and TB. Paper presented at *CMS-MITACS joint conference*, 31 May – 3 June 2007, University of Manitoba, Winnipeg, Canada.
2. Magombedze G, Garira W, Mwenje E. In-vivo mathematical study of co-infection dynamics of HIV-1 and Mycobacterium Tuberculosis. *Journal of Biological Systems* 2007; accepted.

HIV and drug therapy

3. Lungu E. Treatment of HIV/AIDS with imperfect drugs and behavioural implications. Paper presented at South African Mathematical Sciences conference, 26 November – 3 December 2007, Windhoek, Namibia.
4. Magombedze G, Garira W, Mwenje E. Modelling the immuno-pathogenesis of HIV-1 infection and the effect of multi-drug therapy: the role of fusion inhibitors in HAART. *Journal of Mathematical Biosciences and Engineering* 2007; accepted.
5. Ouifki R, Welte A, Pretorius C. A model of HIV infection with two strains and CTL response under structured treatment interruptions. *South African Journal of Science* 2007: submitted.
6. Ouifki R, Witten G. A model of HIV-1 infection with HAART therapy and intracellular delays. *Discrete and Continuous Dynamical Systems* 2007; 8(1): 229-240.

TB

7. Uys P. A threshold value for the time delay to TB diagnosis. Poster: 38th Union World Conference on Lung Health, 8-12 November 2007, Cape Town, South Africa.

Male circumcision

8. Auvert B, Kahn J, Koremromp E, Lloyd-Smith J, Helleringer S, Taljaard D, Sitta R, Hargrove J, Williams B, Marseille E. Cost of the roll-out of male circumcision in sub-Saharan Africa. In Male Circumcision: The Cutting Edge of HIV Prevention: *Proceedings of the 5th Conference of the International AIDS Society (IAS)* 22-25 July, Sydney, Australia.

HIV prevalence

9. Humphrey JH, Nathoo KJ, Hargrove JW, Iliff PJ, Mutasa K, Moulton LH, Chidawanyika H, Malaba LC, Zijenah LS, Zvandasara P, Ntozini R, Zunguza CD, Ward BJ, ZVITAMBO study group. HIV-1 and HIV-2 prevalence and associated risk factors among postnatal women in Harare, Zimbabwe. *Epidemiology and Infection* 2007 135: 933-942.
10. Hargrove JW, Williams BG. Income inequality and HIV prevalence. Response to: Piot P, Greener R, Russell S. Squaring the circle: AIDS, poverty and human development. *PLoS Medicine* 2007 4(10): e314. doi:10.1371/journal.pmed.0040314

HIV incidence

11. Hargrove JW, Humphrey JH, Mutasa K, Parekh BS, McDougal JS, Ntozini R, Chidawanyika H, Moulton LH, Ward B, Nathoo K, Iliff PJ, Kopp E and the ZVITAMBO Study Group. (2008) Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay *AIDS*; 22, 511-518.
12. Tavengwa NV, Piwoz EG, Iliff PJ, Moulton LH, Zunguza CD, Nathoo KJ, Hargrove JW, Zvitambo Study Group and Humphrey JH. (2007) Adoption of safer infant feeding and postpartum sexual practices and their relationship to maternal HIV status and risk of acquiring HIV in Zimbabwe. *Tropical Medicine and International Health*; 12(1), 97-106.
13. Welte A. Relating Incidence to 'Recent Infection' Prevalence. *South African Journal of Science* 2007: submitted.
14. McWalter T. & Welte A. Relating recent infection prevalence to incidence with a sub-population of non-progressors. *Statistics in Medicine* (submitted).

Continuous-time population models

15. Bacaer N, Ouifki R. Growth rate and basic reproduction number for population models with a simple periodic factor. *Mathematical Biosciences* 2007; 210: 647-658.

Tsetse and trypanosomiasis

16. Bett B, Randolph TF, Kitala P, Gathuma J, Hargrove J, Vale G, McDermott J. Using a mathematical model to predict the impact of a synthetic tsetse repellent on trypanosomiasis transmission in cattle when used alone or in integrated strategies. *Proceedings of the*

International Scientific Council for Trypanosomiasis Research and Control (ISCTRC) Luanda, Angola, 1-5 October, 2007 (in press).

17. Bett B, Randolph TF, Irungu P, Nyamwaro S, Murilla G, Kitale P, Gathuma J, Hargrove J, Vale G, McDermott J. An assessment of the impact of a synthetic tsetse repellent technology on the incidence of trypanosomosis in cattle managed under pastoral production systems in Kenya. Proceedings of the *International Scientific Council for Trypanosomiasis Research and Control (ISCTRC) Luanda, Angola, 1-5 October, 2007 (in press).*

Cellular regulation studies

18. A. Roudneff, R. Ouifki, C.G. Coraci P. Malta and K. Pakdaman "Transition layer equations for delayed monotone positive cyclic feedback systems" (submitted for publication to *Journal of Differential Equations*).
19. R. Ouifki and K. Pakdaman "Small delay induced oscillations in systems of differential equations with state dependent delay" (submitted for publication to *Journal of Mathematical Analysis and Applications*).