Modelling the contributions of malaria, HIV, and malnutrition to a decline in paediatric iNTS disease, Malawi

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Introduction

- Estimated **1.9 M cases and 388,350 deaths** p.a. from iNTS disease in Africa (57% of global burden). 68% of this burden falls on under 5s in Africa
  Ao, Feasey, Gordon, Keddy, Angulo and Crump, EID 2015

- Recent reports of a **decline in iNTS disease** from Kenya and Gambia have emphasised an association with malaria control

- **HIV and malnutrition** are independent risk factors in children

- iNTS disease is **temporally associated with the rainy season**; severe acute malnutrition (SAM) and malaria are also seasonal

- **Multiple interventions** in Malawi could have impacted on decrease in iNTS
  - indoor residual spraying / bednets
  - fertiliser subsidy programme
  - scale up of ART

MLW paediatric blood culture service at Queen Elizabeth Central Hospital 2001-2010

- 49,000 blood cultures taken from children over 9 years
    - <16 years old
    - Febrile / malaria slide negative
    - Afebrile, but clinical suspicion of severe sepsis
    - Malaria slide positive, but critically ill or not responding to antimalarials

    - 10,265 (21%) grew pathogens

    - **3,105 NTS isolates (30%)**

    - **61,320/243,000 (25%) of malaria slides** from febrile children attending hospital positive for *P. falciparum* over the same period

A decline in paediatric iNTS disease in Blantyre

- 77% total decline since peak in 2002

- 12% year on year decline since 2002
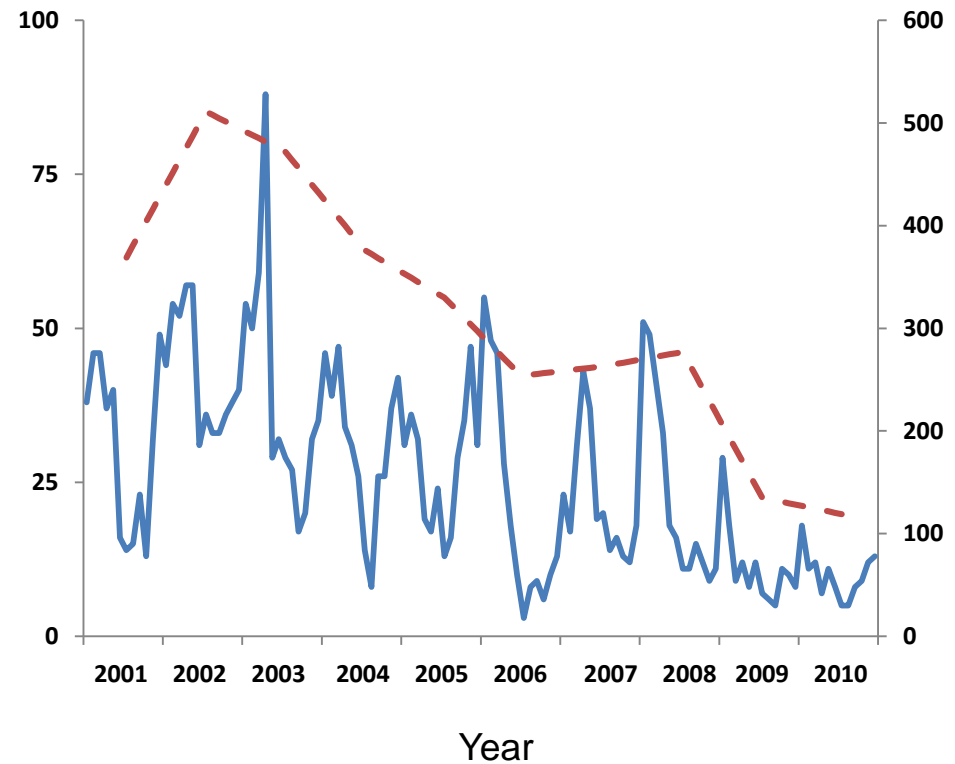
Changes in malaria incidence in Blantyre

- Significant decline between 2001 and 2004

- No significant change from 2005-2010
  - Similarly static figures for cerebral malaria and asymptomatic parasitamia in Blantyre
 - Similar to WHO country-wide data
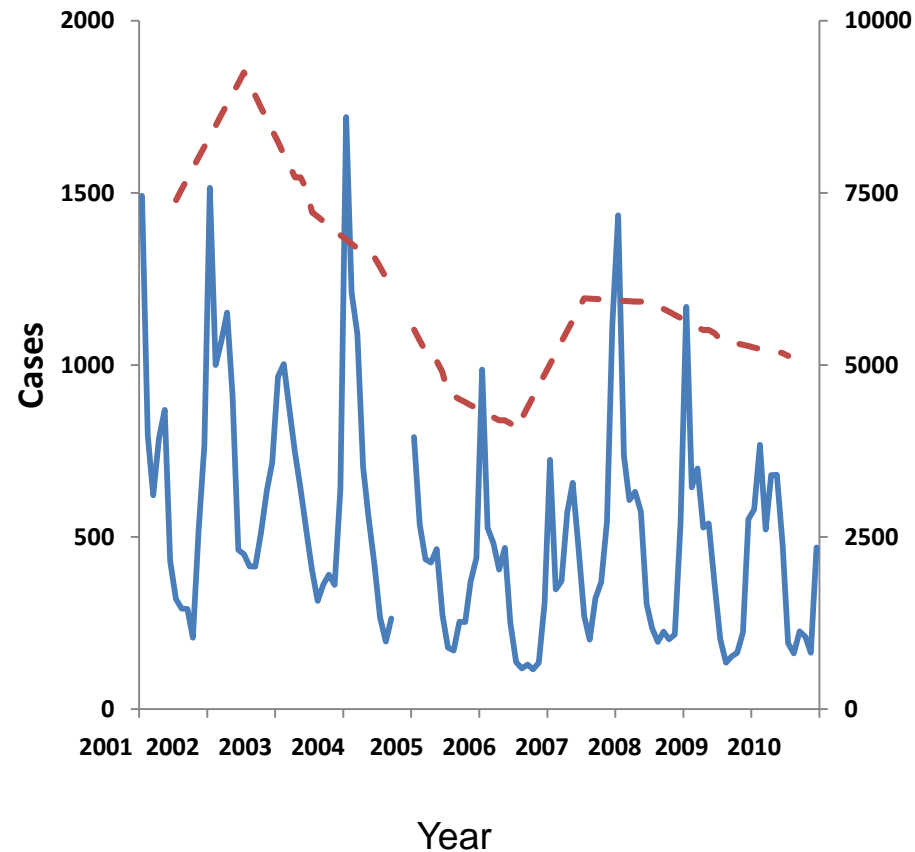
Untreated HIV in children <3 in Blantyre

HIV-infected children

- Childbirth in Blantyre

- Prevalence of HIV infection in pregnancy (22% →16%)

- PMTCT: 1% p.a. fall in vertical transmission, from 18% in 2006 to 14% in 2010
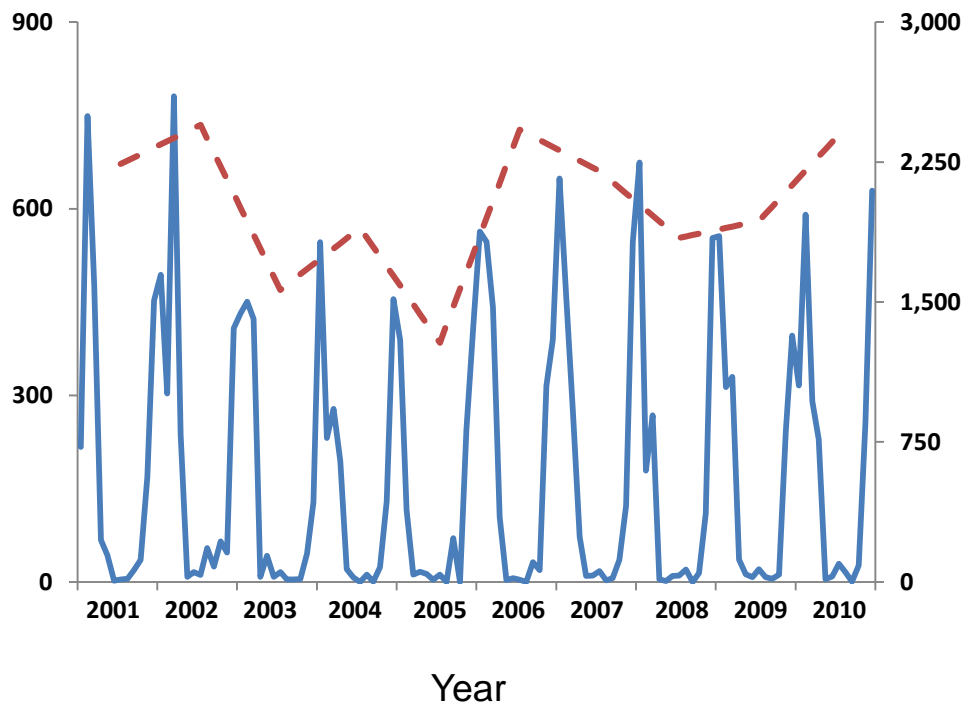
Impact of ARVs on children

- ART programme started in 2006 and reached 30% coverage by 2010

- 70% protection from iNTS on ART

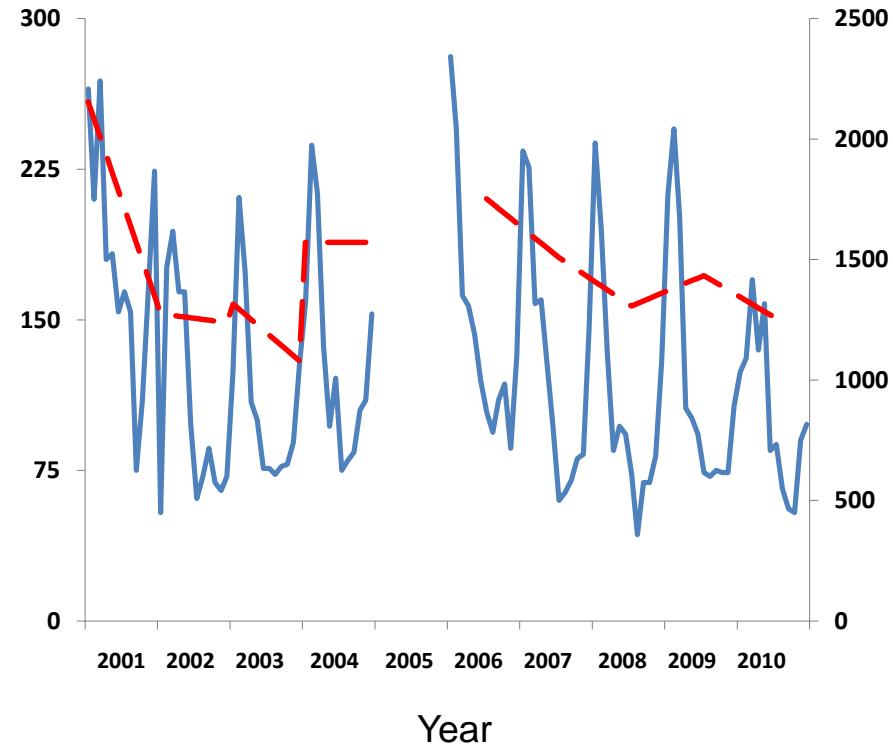- Mortality from HIV 30% p.a. in first 3 years of life if not on ART
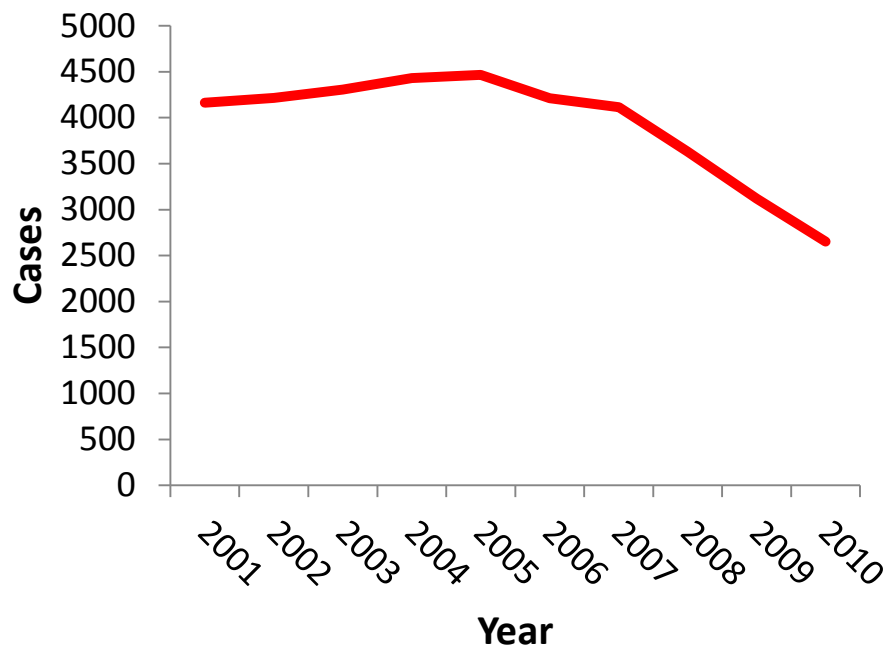
No significant change in rainfall or nutritional rehabilitation unit admissions 2001-10
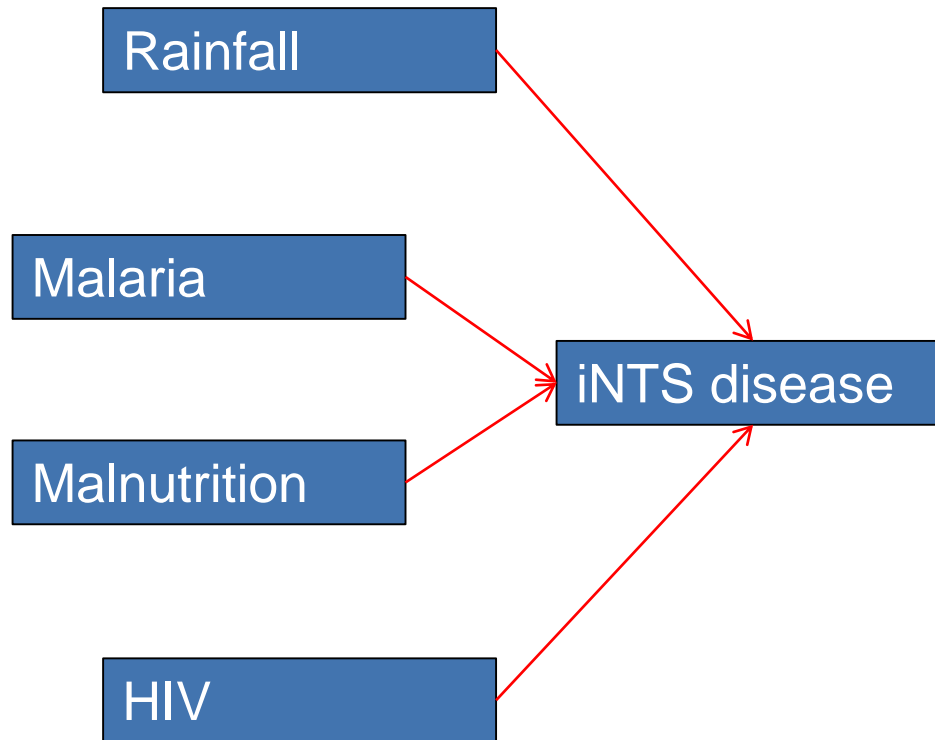
Trends in Rainfall (mm)

Year

Blantyre Meterological Office

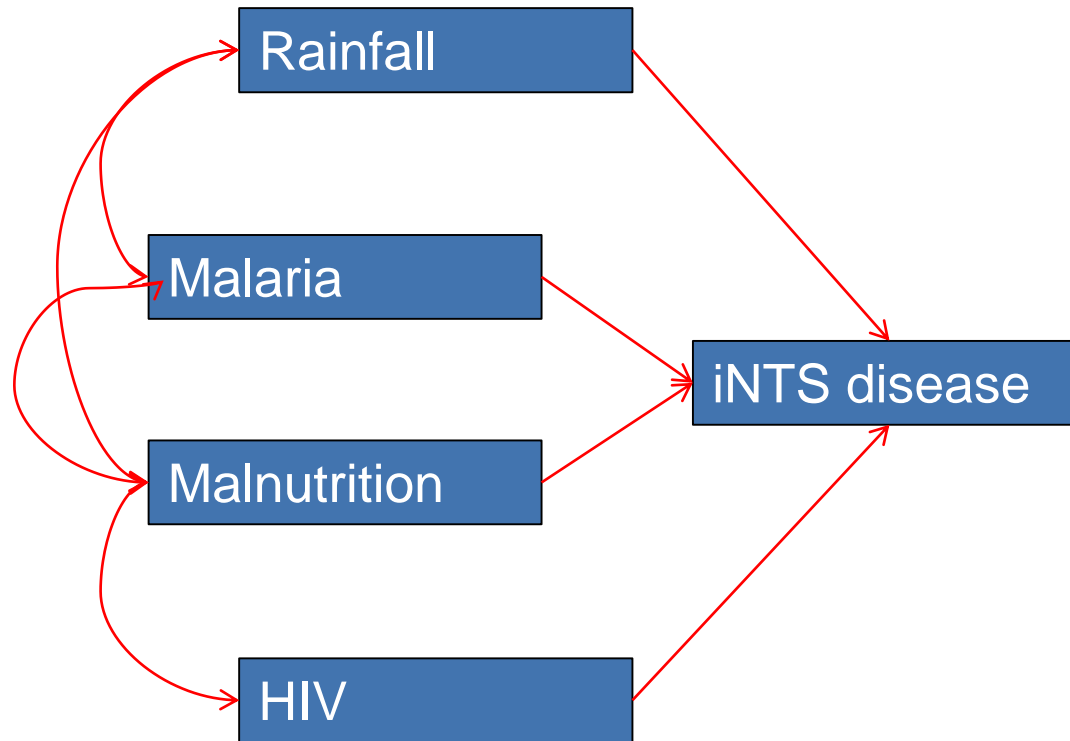### Trends in NRU admissions

Year

weight for height < 70% of the NCHS reference median
and/or nutritional oedema,
and/or MUAC < 110 mm

Multivariable Regression analysis

- Multivariable regression models assume independence of variables
- But risk factors for iNTS disease are interrelated

Rationale for using Structural Equation Modelling

- SEM allow the possibility of exploring an indirect association between a hypothesised variable and the outcome variable through additional variables
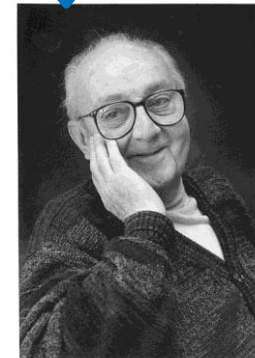
Malnutrition

Rainfall

HIV

Malaria

iNTS

Structural Equation Modelling (SEM)

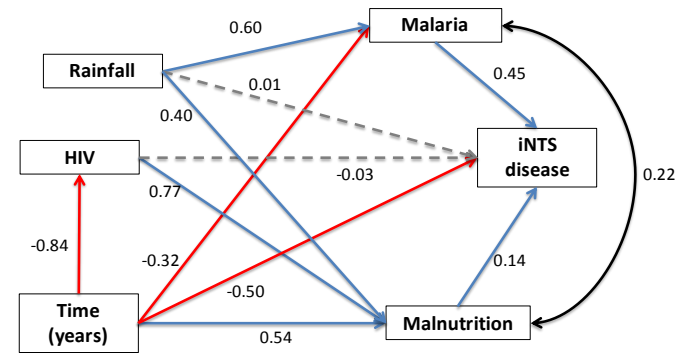# Structural Equation Modelling (SEM)


All models are wrong, but some are useful

George EP Box

SEM

- Bayesian network as a hypothesised model of nodes (variables) and lines (probability of relationship)

- Each line is attributed
  - statistical significance indicating probability of relationship
  - standardised regression coefficient estimate, indicating relative strength of association

- Explore **indirect association** between a variable (node) and the outcome variable (node) through additional variables (nodes)

- **Directionality of lines** can impute causality of significant relationships

Model of iNTS 2002-10: including monthly seasonal variation
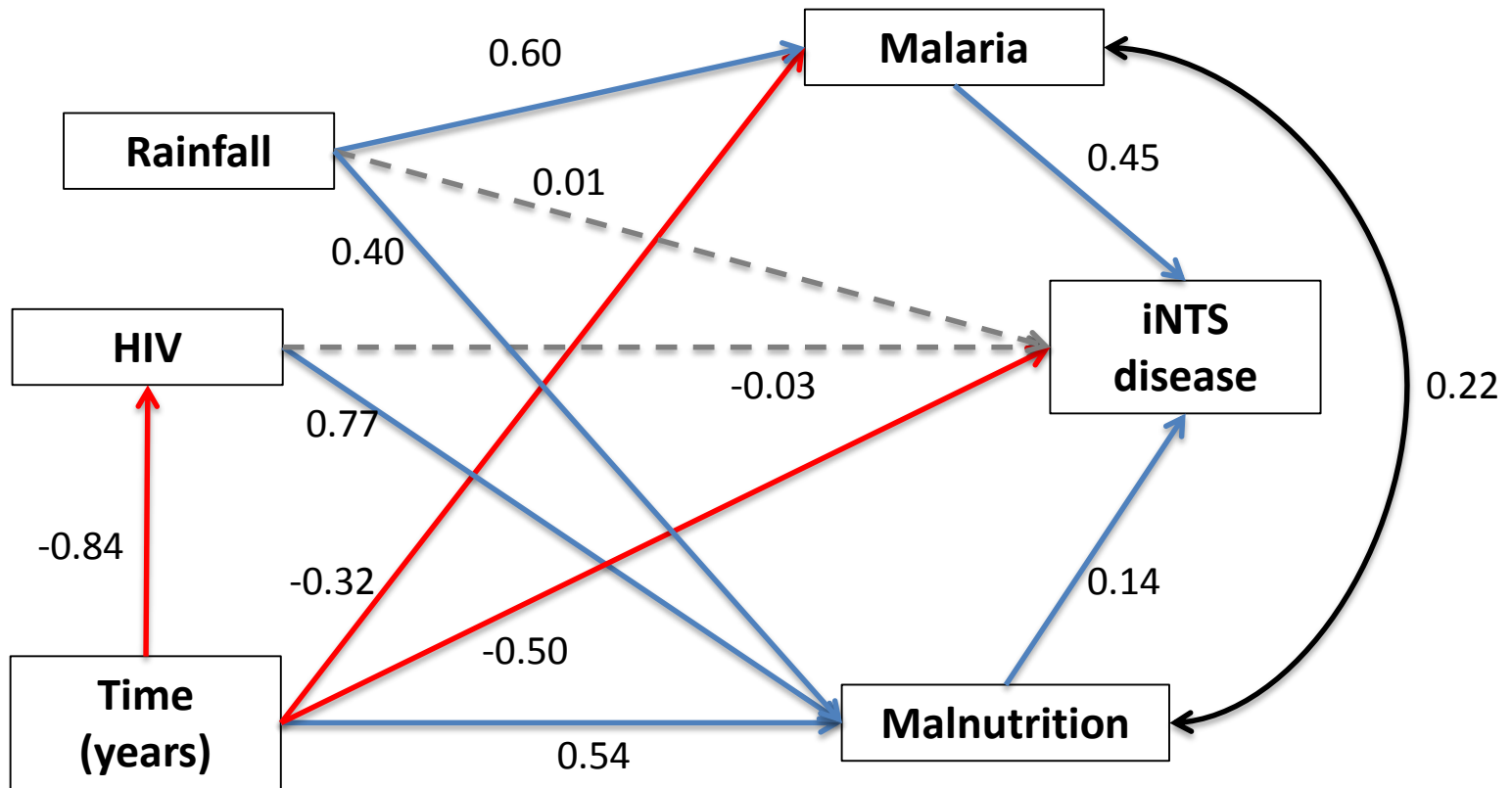
Numbers are standardised regression coefficients from SEM model fit.

———▶ indicates statistically significant *positive* relationships

———▶ indicates statistically significant *negative* relationship

- - - ▶ indicates statistically *non*-significant relationships

◀———▶ indicates a correlation

# Model of iNTS 2002-10: including monthly seasonal variation
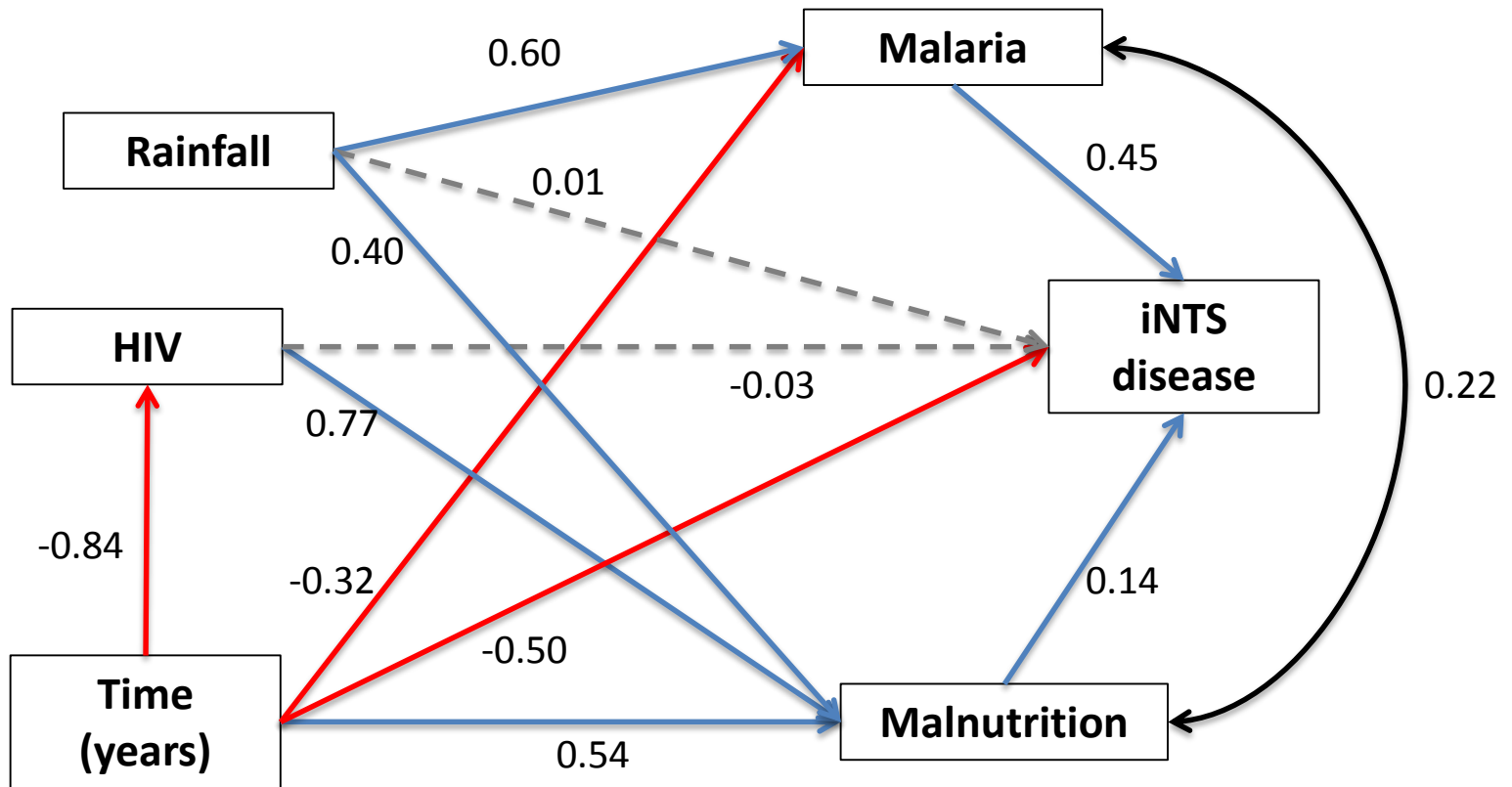
Independent significant contributions to iNTS from malaria and malnutrition

Rainfall no direct effect on iNTS but a strong effect via malaria and malnutrition

HIV no direct effect, but an effect via malnutrition ??

Time effects

RMSEA = 0.067 (90% CI: <0.001-0.188).

Data smoothed (12-month rolling average) to remove monthly seasonality
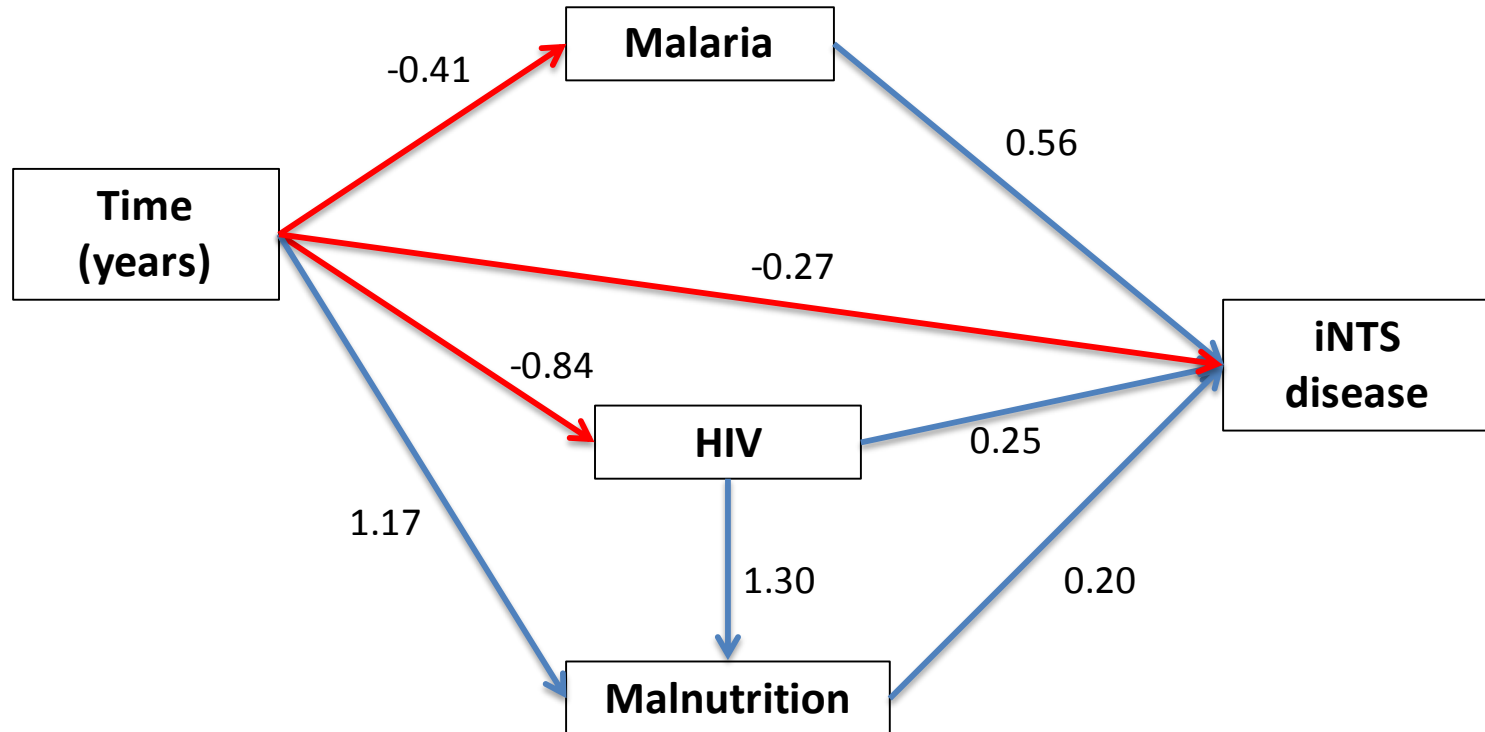
Rainfall no longer contributes

Malaria and malnutrition remain significant, no correlation

Additional significant year-on-year direct effect of HIV on iNTS

Continued strong relationships between HIV and malnutrition

Continued time effects

RMSEA <= 0.001 (90% CI: <0.001-0.162)

Conclusions

- Complex seasonal and year-on-year inter-relationships between multiple risk factors – need to understand both

- Decline in iNTS disease observed in Malawi attributable to several different public health interventions leading to reductions in:
  - Malaria
  - HIV
  - Severe acute malnutrition

- **Understanding the direct and indirect impacts of public health programmes on iNTS disease in Africa is critical to plan and evaluate interventions**
  - Not as simple as malaria control
  - "Unexplained" effects over time after all variables considered indicates other influences which might not be modifiable

Thanks to

- Prof Brian Faragher and Arthur Kang'ombe (modelling)

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