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

Nick Feasey Brian Faragher, Melita Gordon & Robert Heyderman
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)

Trends in NRU admissions

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

Blantyre Meterological Office
Multivariable regression analysis

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

Risk factors:
- Rainfall
- Malaria
- Malnutrition
- HIV

Result:
- iNTS disease
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

HIV

Malaria

Rainfall

iNTS
Structural Equation Modelling (SEM)
Structural Equation Modelling (SEM)

All models are wrong, but some are useful

George EP Box
SEMs

- 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
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 $\leq 0.001$ (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
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