NSP modelling with the EndTB model

Meeting with Global Fund - 16th Dec 2022

Roel Bakker
KNCV, LSHTM

Junior Modellers

- Demelash Assefa Abebe
  - Education: Master's degree in public health concentration in Epidemiology
  - Current position:
    - Regional Technical Officer KNCV Tuberculosis Foundation, Adherence Support Coalition to End TB (ASCENT) Project
  - Experience in working with TIME Impact model: calibrating the model

- Liza de Groot
  - Master's degree (cum laude) in Health Sciences (specialization Infectious Diseases and Public Health)
  - Current position:
    - Junior researcher at KNCV Tuberculosis Foundation
  - Followed course at KNCV in Modelling Infectious Disease Dynamics

Who is Roel Bakker?

- modeller of infectious disease dynamics
  - KNCV Tuberculosis Foundation January 2022 -
  - TB Modelling Group, London School of Hygiene and Tropical Medicine (LSHTM, London, UK) 2016 -
  - Infectious Diseases Section, dept Public Health, Erasmus MC Rotterdam (1995 - 2020)
    - individual-based models of infectious diseases (STDSIM (HIV/SOA), Wormsim (parasitic worm infections))
    - deterministic models (NTDs, VL, TB)
  - publications: https://scholar.google.nl/citations?user=GKPr_tAAAAAJ&hl=en
- lecturer computer science, Rotterdam University (2001-2014, 2019-2020)
  - bioinformatics, data science, machine learning, AI
- background
  - PhD in physiology of University of Amsterdam
  - ABN Amro Bank: technical IT-specialist, IT-architect (1988-2001)
  - extensive experience in teaching and programming (Fortran, Pascal, Forth, C, Java, Python, R)

EndTB is based on the existing TBvax model

The **EndTB model** is a dynamic simulation model of Mtb transmission and TB progression in a population structured by age, TB stage, HIV status, RISK, SES, TB Vaccine status (developed by Roel Bakker)

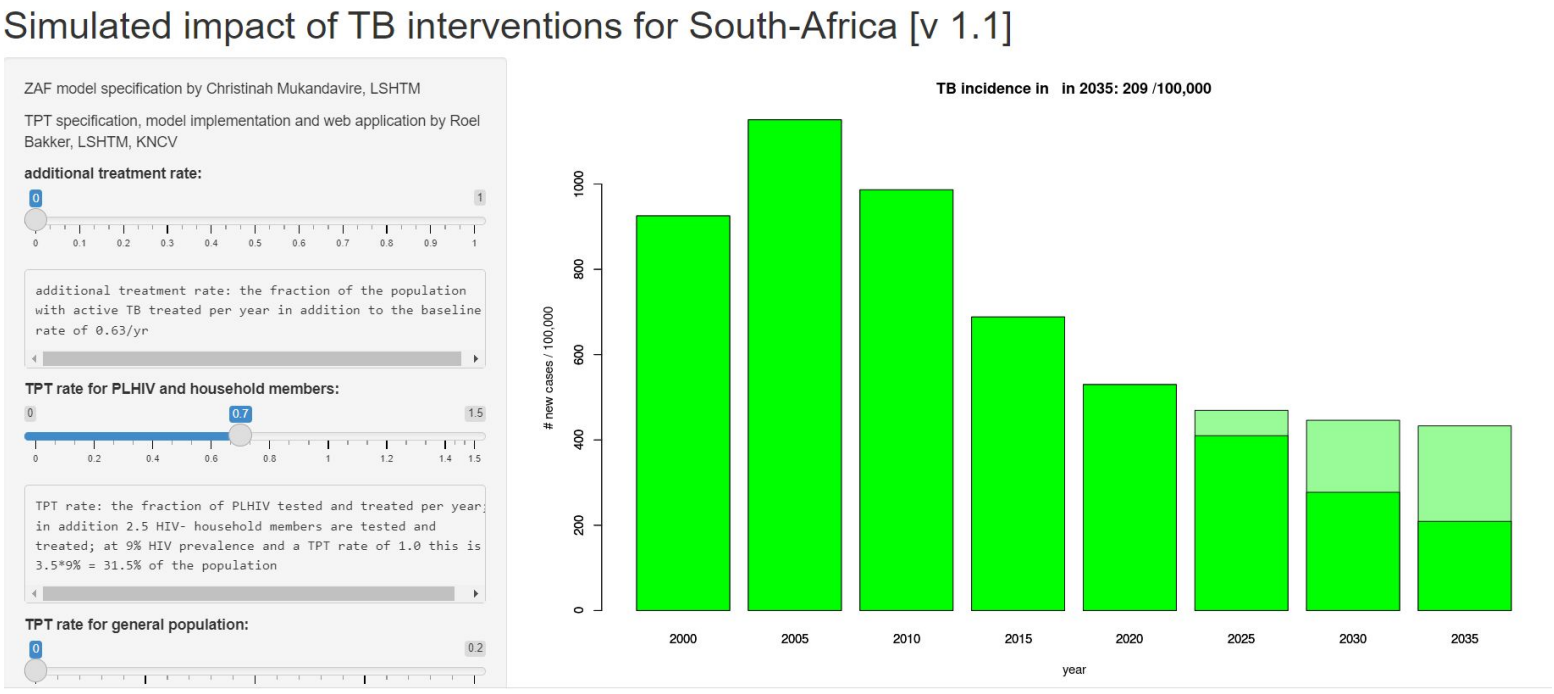
EndTB is based on the **TBvax** model that is used by the TB Modelling group (prof Richard White) at LSHTM since 2020 in a project funded by WHO and BMGF to estimate the impact of TB **vaccines** on Mtb transmission and TB progression

The **model specification** is in the appendix of a paper submitted to Lancet Global Health (and available on MedrXiv now at The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study | medRxiv)

User friendly web version of EndTB

https://roelb54.shinyapps.io/TBvaxdemo/

[may be slow in starting up and takes 10-15 secs for a simulation run]

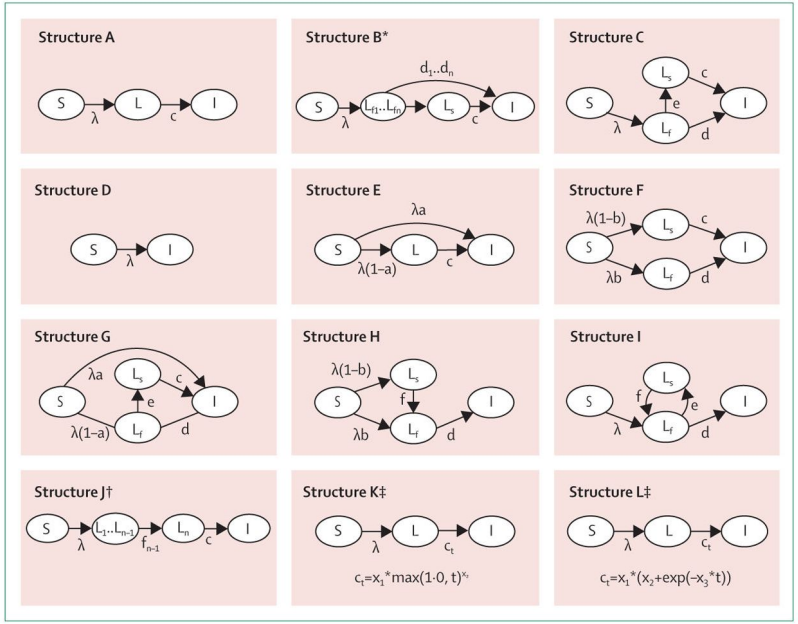


Why EndTB?

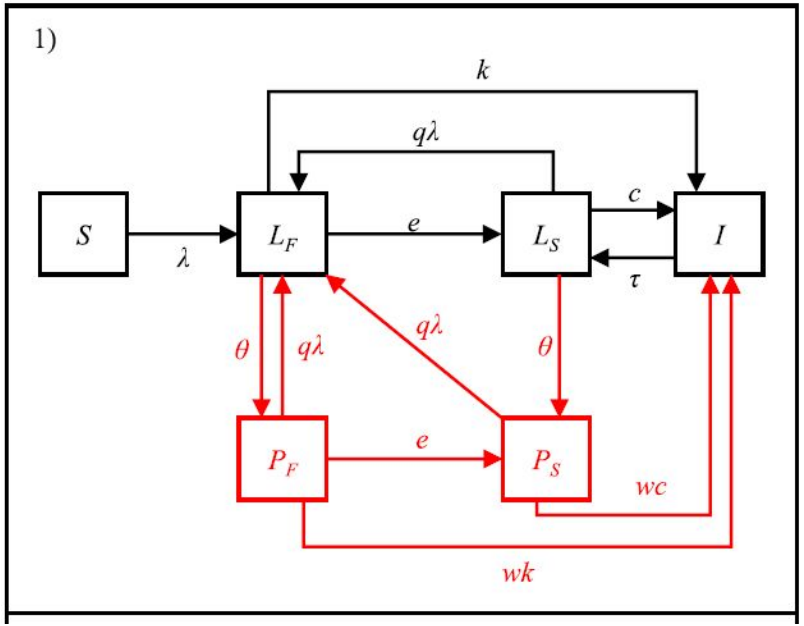
- make using transmission models more accessible to in-country modellers / epidemiologist
- (for now) expert modellers will do calibration (parameter estimation using data)
- train in-country modellers
- pilot this approach in Namibia
- develop e-learning
- extend to other countries
- collaboration with TB Modelling Group at LSHTM

EndTB model design - 1. background

Many assumptions about TB natural history



[from the 2018 paper by Nick Menzies]



[from the 2020 paper by Sumner and White on TPT]

EndTB model design - 2

Model requirements

- flexible definition (not hard coded) of TB natural history
- as most HIV deaths are due to TB:
  - include HIV (undiagnosed, diagnosed, on ART, ART suppressed) natural history

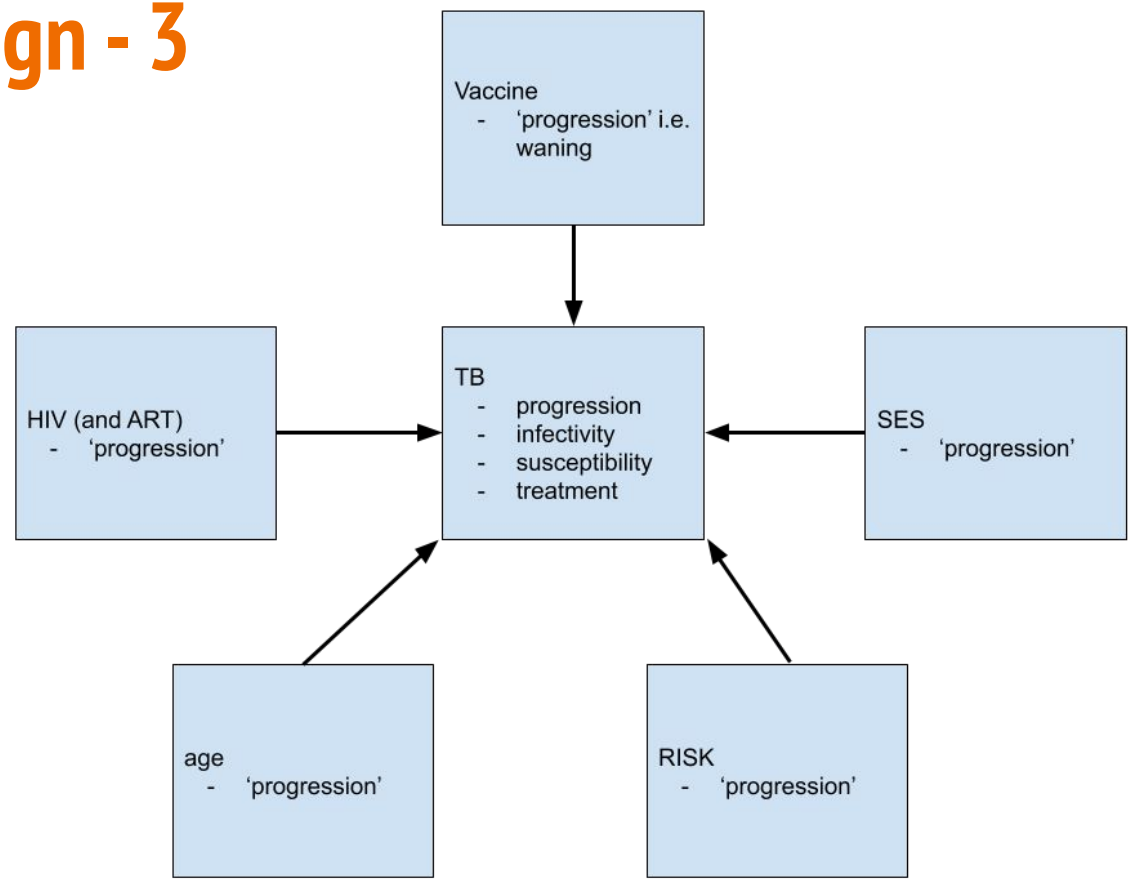
How to include HIV?

- as a separate ‘dimension’ i.e. to enable simple specification of HIV natural history
- enhanced TB progression in HIV+ by using HIV dependent parameters

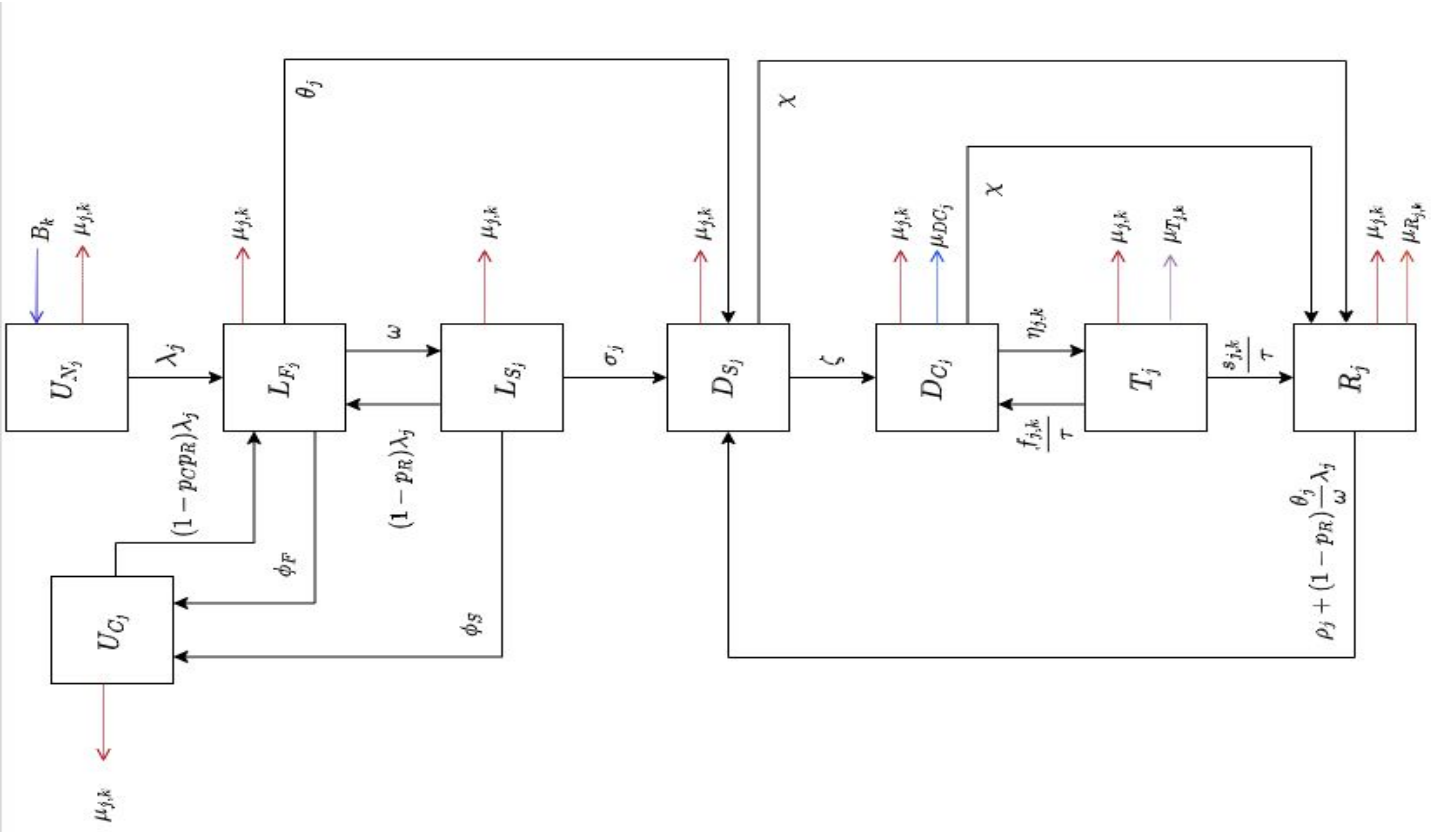
EndTB model design - 3

The full TB model includes options to define **dependencies** (see right panel), so any TB parameter may depend on any of:
age, **HIV**, **RISK**, **SES**, and **Vx**.

(and even reverse dependencies are possible)



EndTB: example TB natural history (as used in TBvax)



example TB natural history definition

```
<TB>
  <TB.stages>
    <stage name="Un" fraction.at.birth="1"/>
    <stage name="Uc"/>
    <stage name="Lf"/>
    <stage name="Ls"/>
    <stage name="Ds"/>
    <stage name="Dc"/>
    <stage name="T"/>
    <stage name="R"/>
    <stage name="TBdead"/>
    <stage name="TBHIVdead"/>
    <stage name="Rdead"/>
    <stage name="RHIVdead"/>
  </TB.stages>
```

example TB state transition definition

```
<transition.matrix>
  <transition from="Lf" to="Ls" rate="omega"/>
  <transition from="Lf" to="Uc" rate="phiF"/>
  <transition from="Ls" to="Uc" rate="phiS"/>
  <transition from="Ds" to="Dc" rate="zeta*(1+atheta*th1)"/>
  <transition from="Ds" to="R" rate="chi/(1+aHIVslowrecov*th1)"/>
  <transition from="Dc" to="R" rate="chi/(1+aHIVslowrecov*th1)"/>
  <transition from="Dc" to="TBdead" rate="sage*muDc*(!HIVpos)"/>
  <transition from="Dc" to="TBHIVdead" rate="sage*muDc*(1+aHIVdeath*HIVx)*HIVpos"/>
  <transition from="R" to="Rdead" rate="sage*muK*(!HIVpos)*0.22"/>
  <transition from="R" to="RHIVdead" rate="sage*muK*(1+aHIVdeath*HIVx)*HIVpos*0.22"/>
</transition.matrix>
```

EndTB model in summary

User benefits

- the model is a multi-purpose **tool** for infectious disease dynamics
- the user defines the model
  - age groups
  - TB natural history and transmission
  - dependencies by HIV, RISK, SES and TB Vaccine
  - age mixing (contact matrices based on PolyMod study)

Technical benefits

- simple and fast due to matrix operations

Technical details - 1

Performance

- The rate of change (of all variables) can be calculated by simple **matrix multiplications**
- A simulation run of 150 years with a model with about 50,000 (82 age groups * 10 TB states * 2 SES * 10 HIV/ART * 3 Vx) state variables (i.e. 50,000 differential equations) requires just 20 - 40 seconds

Complexity

- Basically all that happens in the simulation are state transitions:
  - transmission (Un -> Lf)
  - progression (Lf -> Ls)
  - even incidence data can be expressed as state transitions
    - HIV negative -> HIV+
    - ART (HIV+ -> ART)
    - Vx implementation: (unvaccinated -> protected)

Technical details - 2

- In an SIR model defined by (where the dot on top of S, I and R indicate the time derivative i.e. dS/dt etc.):

$$\dot{S} = -\beta \cdot I \cdot S/N$$
$$\dot{I} = \beta \cdot I \cdot S/N - \gamma \cdot I$$
$$\dot{R} = \gamma \cdot I$$

with $\lambda = \beta \cdot I/N$

- The time derivatives of S, I and R can be calculated by:

$$\begin{bmatrix} \dot{S} \\ \dot{I} \\ \dot{R} \end{bmatrix} = \begin{bmatrix} -\lambda & 0 & 0 \\ \lambda & -\gamma & 0 \\ 0 & \gamma & 0 \end{bmatrix} \cdot \begin{bmatrix} S \\ I \\ R \end{bmatrix}$$

- i.e. a multiplication of a matrix and a vector (S, I, R)
  (that could just as well be a matrix with age groups in columns)
- this is the basis for all calculations in the TB Vx model (though the matrices are larger e.g. 648 rows x 648 columns for parameter matrices and 648 rows by 82 columns for the state variables

TIME vs EndTB - 1

TIME

- **fixed TB natural history** (basically S-L-I-N plus additional for DR TB, on treatment etc)
- TB transmission due to aggregated force of infection distributed proportionally over population (though age dependent susceptibility) ; **no use of contact matrices by age group**
- **no facilities for parameter estimation** (?) though Katherine Horton used a research version of TIME with ABC MCMC in https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0000784

EndTB

- **flexible TB natural history** (see Clark et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study | medRxiv)
- TB transmission takes into account **contact matrices by age group** (based on PolyMod study; see Keisha Prem et al)
- **parameter estimation**: Demonstrating multi-country calibration of a tuberculosis model using new history matching and emulation package - hmer | medRxiv and/or ABC MCMC and/or optimization
- fitted parameters sets available for 100+ LMIC countries (see Clark et al.)
- we have a POC of automated scenario optimization (see presentation for BMGF)

TIME vs EndTB - 2

Comparison of TIME with EndTB

- we are working on comparing TIME with EndTB
  - for one or two LMIC countries
  - by configuring EndTB to ‘emulate’ TIME and switching on features (such as using contact matrices in TB transmission)

User friendly web version of EndTB

Based on previous work at Erasmus MC

https://erasmusmcmgz.shinyapps.io/dissemination/

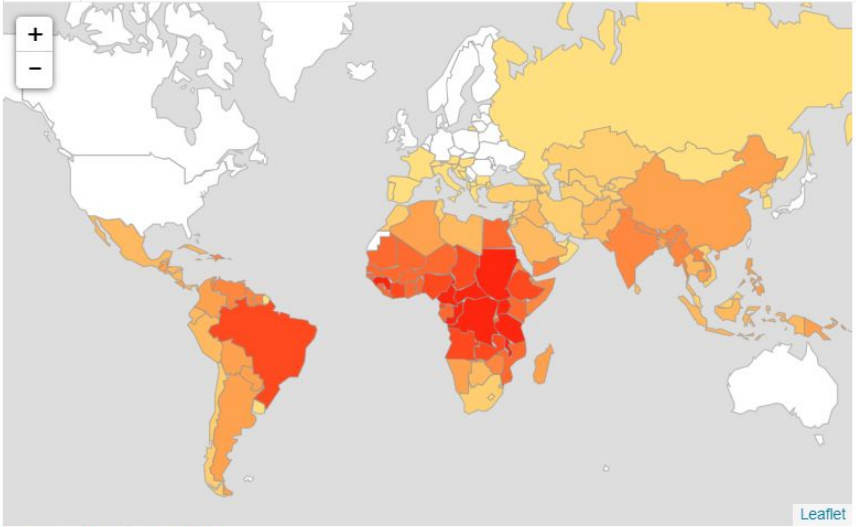
Health and economic impact of achieving the WHO targets for control and elimination of London Declaration NTDs

Erasmus MC University Medical Center Rotterdam

BILL & MELINDA GATES foundation

ALL | LF | ONC | SCH | STH | TRA | CHA | HAT | LEP | VL

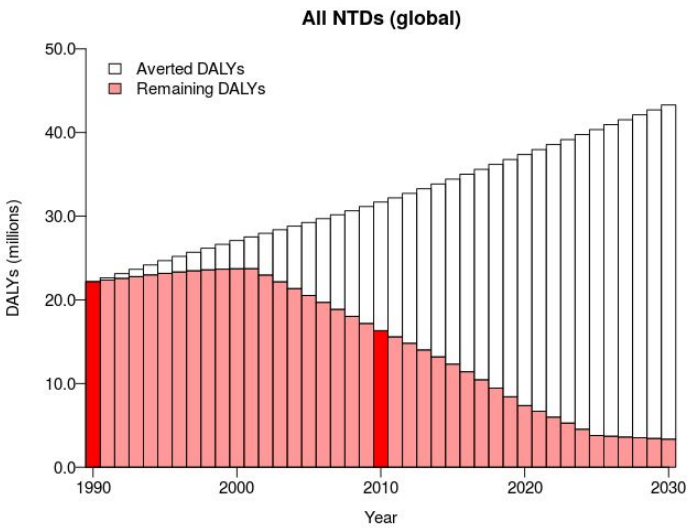
About



Number of NTDs in 2010

0 1 2 3 4 5 6 7 8 9

DALY



Period	DALYs (millions)			Cost (billions I$)
	No intervention	Remaining	Averted	Averted
2011-2020	347.4	117.0	230.4	273.8
2021-2030	406.3	43.8	362.5	348.9
2011-2030	**753.7**	**160.8**	**592.9**	**622.7**

Questions?