Epidemiological modelling via back-calculation

Investigating the underlying pattern of leprosy incidence.

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Outline

Back-calculation

Leprosy

Time-period distributions

Back-calculation analyses of leprosy

Back-calculation

References and Applications

- References
  - Brookmeyer and Gail (1988). A method for obtaining short-term projections and lower bounds on the size of the AIDS epidemic. *J. Am. Stat. Ass.* **83**:301–308
  - Egan and Hall (2015). A review of back-calculation techiniques and their potential to inform mitigation strategies with application to non-transmissable acute infectious diseases. *J. R. Soc. Interface* **12**:20150096
- Applications
  - HIV/AIDS
  - BSE
  - vCJD
  - cancer
  - Bio-terrorism: required prophylaxis, locating source

Back-calculation

Basic

Given information on incidence and the incubation period distribution, inferences can be made about the occurrence of infections...

For discrete time periods:

$$D_i = \sum_{j=1}^{i} I_j f_{i-j}$$

D_i exp. number of new diagnoses in the i^{th} time interval

I_j exp. number of infections in the j^{th} time interval

f_{i-j} prob. that the time between infection and diagnosis is $i - j$ time intervals

Leprosy

- Bacterial disease of the skin & nerves
- Infection curable, but can result in permanent disabilities if left untreated
  - free treatment
- Social stigma
- Diagnosis – of symptomatic cases
  - skin lesions
    - $+$ sensory loss, $\pm$ thickened nerves
  - positive skin smears
    - Not required since 1996 (WHO)
- No leprosy vaccine – yet
  - BCG vaccine – tuberculosis

- Classification

	PB	MB
Lesions	≤ 5	> 5
Treatment	$6 \times$ 2-drug	$12 \times$ 3-drug

- Cannot be cultured
- Hard to catch, most people not susceptible
- Transmission? **droplets**, close contact
- Wildlife (and environmental?) reservoirs
  - e.g. nine-banded armadillo

History

1873 Hansen discovered *Mycobacterium leprae*

1940s Single drug treatment

1984 Multidrug therapy (MDT) recommended

1991 WHA resolve to eliminate leprosy as a public health problem by 2000

1995 WHO make MDT freely available

2000 WHA global target met, national targets adopted

2008 *M. Lepromatosis* discovered

2011 Armadillo to human transmission

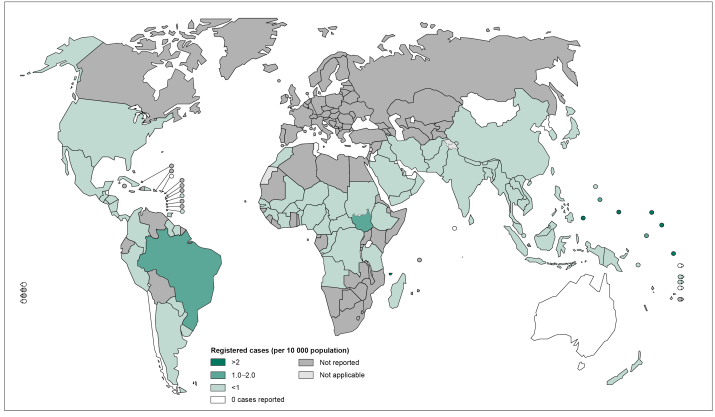
2012 WHO Roadmap
London declaration on NTDs

2013 Bangkok declaration
reduce the number of new cases with grade 2 disability to $< 1/1,000,000$ by 2020

2016 Leprosy in UK red squirrels

Prevalence 2013

Registered cases of leprosy per 10 000 population (prevalence rates), 2013



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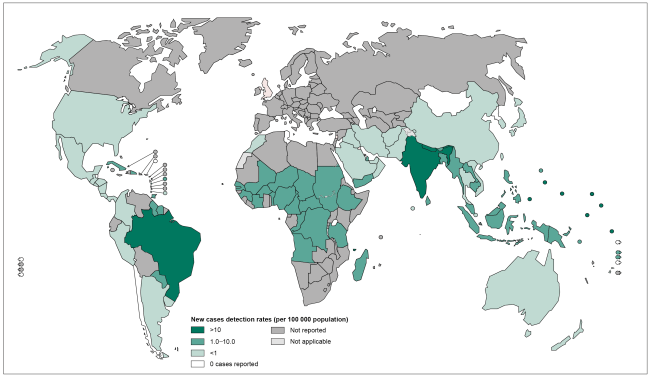
Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Globally, 1 case per 10,000 reached by 2000; but there are countries, and regions within countries, with higher prevalence

New cases 2013

New cases detection rates of leprosy per 100 000 population, 2013



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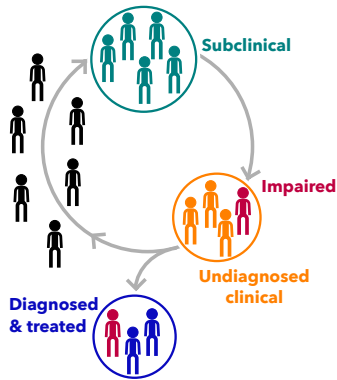
World Health Organization

- $\approx 216,000$ new cases worldwide
- India 127k, Brazil 31k, Indonesia 17k (Nepal 3k+)
- 18 countries $\rightarrow$ 96% of new cases
- 44 countries with ≥ 100 new cases, 84 with ≥ 1.

Mathematical modelling of leprosy

- Long, variable times from
  infection → onset of symptoms → diagnosis
- Endemic
- Diagnosis of clinical cases
  - Reducing detection delay
    - less transmission
    - fewer cases with impairments
- Most readily available data are annual case counts
  - National-level from Weekly Epidemiological Record
  - Brazil state-level online
- Can we use case count data to talk about...
  - underlying transmission?
  - changes in detection success?
    - changes in control programme



Incubation period and detection delay distributions

Parameterisation of IPD and DDD

- Need to know when:
  - infected;
  - symptom onset; and
  - diagnosis.
- Endemic
  - Data from leprosy patients from non-endemic countries
    $\rightarrow$ known exposure periods
  - 49-patient dataset from literature
    - mainly US military veterans
- Larger, and more relevant, datasets just with DD information available, e.g. Meima *et al.* (1999)

IPD and DDD parameterisation

- Data relative to start of exposure period for individual

$$\log L = \sum_{j=1}^{N} \log \text{Prob}\left(o_{1j} < p_{i_j} \leq o_{2j} | t_{i_j}\right) + \log \text{Prob}\left(d_{1j} < p_{d_j} \leq d_{2j} | t_{i_j}, t_{o_j}\right)$$

p_{i_j}, p_{d_j}	incubation period (detection delay) for individual j
t_{i_j}, t_{o_j}	time of infection (onset) for j, uniform within observed range
o_{1_j}, o_{2_j}	start (end) of observed onset period
d_{1_j}, d_{2_j}	start (end) of observed diagnosis period

$$p_i \sim \text{Gamma}(\alpha_i, \beta), \quad p_d \sim \text{Gamma}(\alpha_d, \beta), \quad p_i + p_d \sim \text{Gamma}(\alpha_i + \alpha_d, \beta)$$

Back-calculation

Our leprosy variant

- Two time periods
  - subclinical → clinical
    - *incubation period distribution*
  - clinical → diagnosed
    - *detection delay distribution*
    - **diagnosis success parameters**
- New infections proportional to infectious pool, **q**
  - all undiagnosed, clinical cases
- Equilibrium period
  - diagnostic success is 1
  - **expected annual number of new diagnoses**

- At diagnosis, assign MB cases
  - **proportion MB**
- equilibrium period → pre-data period → *data* & forecast period
- Poisson likelihoods for number of new cases and number of new MB cases
- expectations and simulated observations
- MCMC in Stan via R
- Multiple inference[a]
  - uncertainty in IPD and DDD parameters

[a] used in these analyses, but no longer

Analyses of Brazilian leprosy data

Data

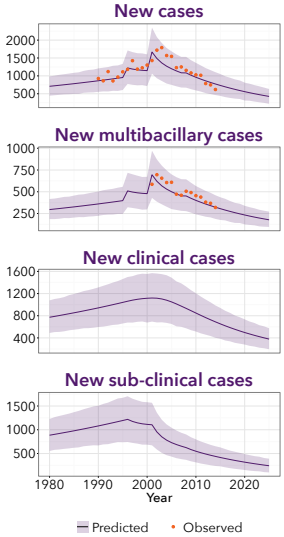
- State level (27 states)
- Annual number of new cases
  - 1990–2012
- Annual number of new MB cases
  - 2000–2012
- Sources
  - 1990–2012: SINAN database
  - 2013–2014: Govt. health portal

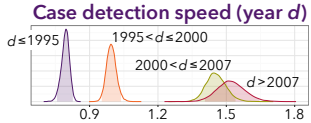
Analyses

- All states, inference about unobserved cases and future probability
- 'What if. . . ?' scenario
  - changing diagnostic success
- Model comparison

State-level analysis for Brazil

Results for Espírito Santo



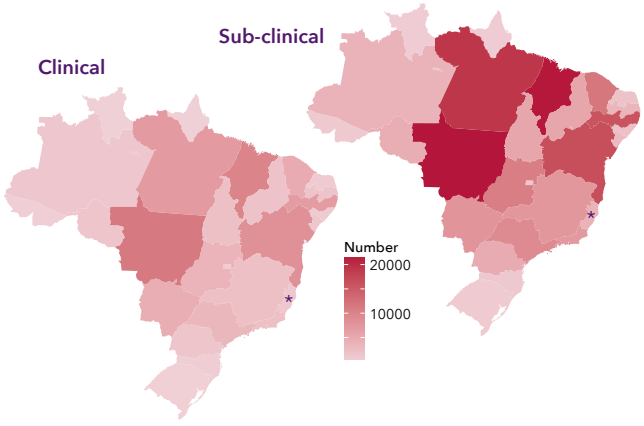


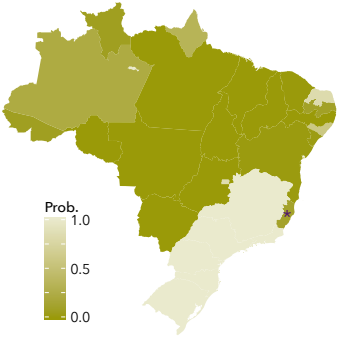
- Estimates of time delays between onset of disease and diagnosis for different time periods shown as posterior distributions.
- Diagnostic timeliness improved dramatically post-2000, but there is little evidence of subsequent improvement.
- Findings vary between states.

State-level analysis for Brazil

Underlying case numbers and ‘goal’ assessment

Most probable values of cumulative numbers of undiagnosed cases of leprosy in Brazilian states in 2014

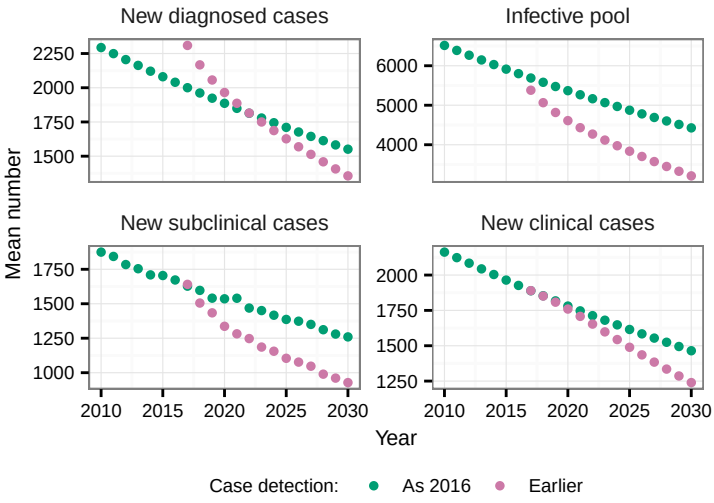




Forecast probability of the new case detection rate in Brazilian states being below 1 per 10,000 in 2020

Impact of changing diagnostic success

Decreasing the mean detection delay by 6 months (Ceará state)

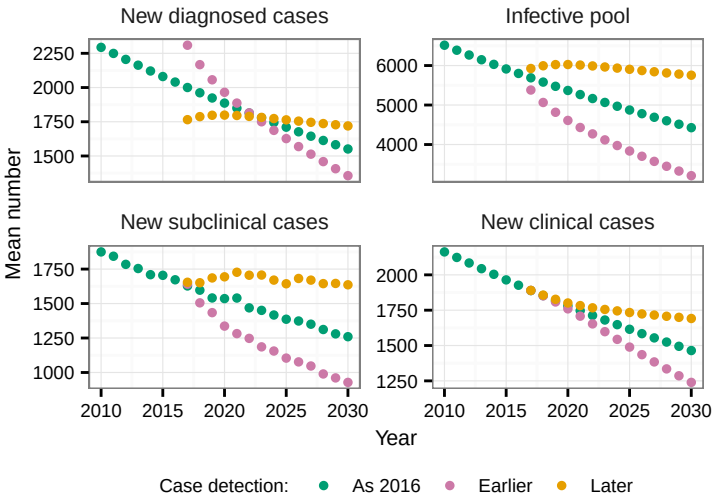


Decreasing delay

- ↑ number of diagnoses
  - persists
- long-term decrease
- ↓ infective pool
  - ↓ subclinical
    - ↓ clinical

Impact of changing diagnostic success

Decreasing, or increasing, the mean detection delay by 6 months (Ceará state)



Decreasing delay

- ↑ number of diagnoses
  - persists
- long-term decrease
- ↓ infective pool
  - ↓ subclinical
    - ↓ clinical

Increasing delay

- opposite effect

Detection delay as a measure of status/progress

- recording/publishing
- veracity over precision

State-level analysis for Brazil

Model comparisons

Four models

- Back-calculation
- SIMCOLEP
  - Erasmus MC
  - Individual simulation
- Deterministic compartmental model
  - UCSF/Yale
  - data from 2001 onwards
- Linear mixed model
  - UCSF
  - data from 2001 onwards

Data

- 4 states
- low–high NCDR in 2014

Compare

- Short-term forecasts
  - exclude data and predict 2012–2014
- Longer-term forecasts
  - trends in NCDR &
    Prob. NCDR $< 10/100{,}000$

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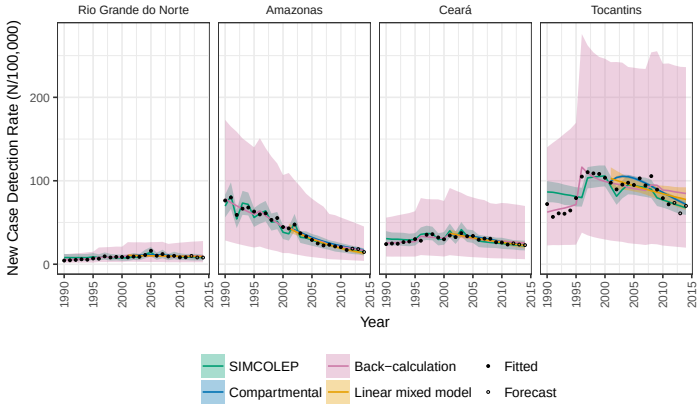
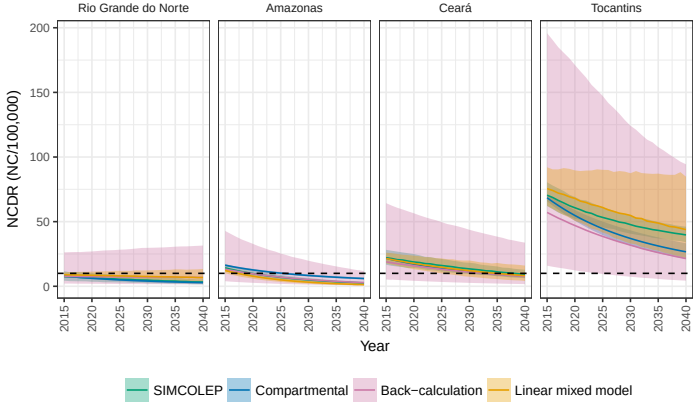
Model comparison: fit and short-term forecasting



nb the variance in the back-calculation results was artificially high, ignore (now being done differently) – the trends are 'the point' here.

State-level analysis for Brazil

Model comparison: long-term NCDR trends



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Summary

Our method...

- can make inferences about underlying numbers of leprosy cases and short-term forecasts
- can consider basic 'what if' scenarios
  - rather than modelling specific interventions (as in transmission models)
- is broadly consistent with other mathematical modelling of leprosy

On-going

- 'Global' forecasting
  - national-level data from WER
  - including G2D data
  - unknown diagnostic effort time periods
- Brazilian state-level data with migration
  - annual migration rates between states approximated from census data
    - assume constant over time
    - assume undiagnosed cases can migrate at these rates
  - thinking about the potential impact of migration on control/elimination programmes

NOVARTIS

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