Practical aspects of backward bifurcation in a mathematical model for tuberculosis

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Outline

• Basics on tuberculosis and BCG vaccine
• Model description
• Original motivation for model and conclusions
• Backward bifurcation
  – Analytic thresholds for existence
  – Practical considerations
Tuberculosis Basics

- Approximately 1/3 of the world’s current population has LTBI
- Exogenous reinfection
- Recovered individuals are susceptible to future infection
Bacille Calmette-Guérin (BCG) Vaccine

- Old, inexpensive, safe and well-tolerated
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- Highly variable efficacy
  - repeated studies in the UK → (60-80%)
  - UK study from 1956-1963 → (84%)
  - Georgia/Alabama study in 1966 → (14%)
  - India in 1979 → (0%)
  - Meta-analysis in 2000 → (71-83%)
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• Protective efficacy wanes with time (10-55 years of protection)
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- Protective efficacy wanes with time (10-55 years of protection)

- Can interfere with the detection of Latent TB
TB Model

\( S = \text{susceptible} \)

\( V = \text{vaccinated} \)

\( E = \text{latently infected} \)

\( E_V = \text{vacc. & latently infected} \)

\( I_T = \text{actively infected \& treated} \)

\( I_{Tc} = \text{actively infected \& untreated} \)

\( R = \text{recovered} \)

\( c = \text{vaccine coverage} \)

\( p = \text{prob. of fast progression} \ (\approx .05) \)

\( d = \text{detection rate (active TB)} \)

\( s = \text{treatment success rate} \)

\( r = \text{detection/treatment success rate (latent TB)} \)

\( p^* = \text{proportion vaccinated} \)

\( 1-p^* = \text{proportion unvaccinated} \)

\( c \) recruitment into the population

\( 1-c \) exogenous reinfection

\( p \) fast progression

\( 1-p \) slow progression

\( c \) vaccine waning

\( 1-c \) infection

\( 1-p \) infection*
TB Model

\( q_1 = \) efficacy preventing initial infection
\( q_2 = \) efficacy preventing fast progression
\( q_3 = \) efficacy preventing slow progression

\( 0 \leq q_1, q_2, q_3 \leq 1 \)

\( \theta_1 = \) factor of susceptibility to exogenous reinfection
\( \theta_2 = \) factor of susceptibility to reinfection after recovery
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Reinfection parameters (ranges from the literature):

- \( \theta_1 \): factor of susceptibility to exogenous reinfection
  
  \( (0, 1), (0.50 - 0.75), 0.25, 0.80 \)

- \( \theta_2 \): factor of susceptibility to reinfection after recovery
  
  \( 4, 1, 0.80, 1.20 \)

\[ 0 \leq \theta_1 \leq 1 \quad 0 \leq \theta_2 \leq 5 \]
The Model

\[ S' = (1 - c)\pi + \omega V - \beta SI - \mu S \]
\[ V' = c\pi - \omega V - (1 - q_1)\beta VI - \mu V \]
\[ E' = (1 - p)\beta SI - (\nu E + \theta_1 p \beta EI) - \mu E, \]
\[ E_V' = [1 - p(1 - q_2)](1 - q_1)\beta VI + (1 - p)\theta_2 \beta RI \]
\[ - [(1 - q_3)\nu E_V + \theta_1 p \beta E_V I] - \mu E_V \]
\[ I_T' = d[((1 - r)\nu E + \theta_1 p \beta EI) + p\beta SI + p(1 - q_2)(1 - q_1)\beta VI \]
\[ + (1 - q_3)\nu E_V + \theta_1 p \beta E_V I + p\theta_2 \beta RI] - \gamma_1 I_T - \mu I_T + \frac{d}{2} I_{Tc}, \]
\[ I_{Tc}' = (1 - d)[((1 - r)\nu E + \theta_1 p \beta EI) + p\beta SI + p(1 - q_2)(1 - q_1)\beta VI \]
\[ + (1 - q_3)\nu E_V + \theta_1 p \beta E_V I + p\theta_2 \beta RI] + (1 - s)\gamma_1 I_T - \gamma_2 I_{Tc} \]
\[ - (\mu + \mu_T)I_{Tc} - d/2 I_{Tc} \]
\[ R' = s\gamma_1 I_T + \gamma_2 I_{Tc} + r\nu E - \theta_2 \beta RI - \mu R \]
Original motivation for the model

Can we establish conditions which justify the discontinuation of mass BCG vaccination?
Original motivation for the model

- treating LTBI
- BCG efficacy

Don’t Vaccinate

- treating LTBI
- BCG efficacy

Vaccinate

Can we establish conditions which justify the discontinuation of mass BCG vaccination?

- Very unlikely that LTBI treatment would outperform mass vaccination
Can we establish conditions which justify the discontinuation of mass BCG vaccination?

- Very unlikely that LTBI treatment would outperform mass vaccination

- WHO TB database to parameterize for 8 countries
- *How much better? & cost-effectiveness*
- LTBI treatment *never* outperforms mass vaccination
- Vaccination is up to 100 times more cost-effective in high prevalence countries
Why look at backward bifurcation?


- Characteristics linked to backward bifurcation in mathematical models
  - Vaccination (imperfect protection, waning, incomplete coverage)
  - Partial immunity and reinfection
  - Limited treatment resources
  ★ All central characteristics of TB epidemiology
  ★ Examine the effect of vaccine efficacy, detecting and treating LTBI

- New diagnostic tests for LTBI: interferon-gamma release assays (IGRA)
  - More accurate than skin testing  ➞ more treatment of LTBI
  - Not confounded by BCG vaccination  ➞ more vaccination
  ★ Potential to push TB towards eradication
Backward bifurcation

\( R_0 \): average number of secondary infections caused by a single infection in a completely susceptible population

- \( R_0 < 1 \) \( \Rightarrow \) disease goes extinct
- \( R_0 > 1 \) \( \Rightarrow \) disease will persist
**Backward bifurcation**

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**Forward (supercritical) bifurcation**

- \( R_0 > 1 \) \( \Rightarrow \) disease will persist
- \( R_0 < 1 \) \( \Rightarrow \) disease goes extinct

- Very low endemic prevalence if \( R_0 \) is slightly greater than 1.
**Backward bifurcation**

\( R_0 : \) average number of secondary infections caused by a single infection in a completely susceptible population

\( R_0 < 1 \) ⇒ disease goes extinct
\( R_0 > 1 \) ⇒ disease will persist

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**Forward (supercritical) bifurcation**

\( R_0 > 1 \) ⇒ disease will persist
\( R_0 < 1 \) ⇒ disease goes extinct

- To eliminate the disease, \( R_0 \) must be reduced to less than \( R_0^* \).
- High endemic prevalence if \( R_0 \) is slightly greater than 1.

**Backward (subcritical) bifurcation**

\( R_0 > 1 \) ⇒ disease will persist
\( R_0 < 1 \) it depends

- To eliminate the disease, \( R_0 \) must be reduced to less than \( R_0^* \).
How can backward bifurcation happen?

• Completely susceptible population *usually* provides maximum infectious potential.

• In general, backward bifurcation is possible in structured populations when “the depletion of the uninfected pool is counteracted by a change in the structure of the population that favors the disease.” — Dushoff *et al.* *JMB* (1998)

• For TB:
  • Exogenous re-infection means latent class can still be infected.
  • Recovered individuals can also be infected and may be as much as *4 times more* susceptible to TB than TB-naïve.
Outline for rest of talk

• Analytic backward bifurcation results for simplified models
  – Model A:
    • no treatment of active TB, universal vaccination, no waning of vaccine protection
    • role of vaccine efficacies on existence of backward bifurcation
  – Model B:
    • no treatment of active TB, no vaccine protection against reactivation of LTBI
    • role of detection/treatment of LTBI on existence of backward bifurcation

• Numerical backward bifurcation results for the full model
  – Compare to results for Models A and B

• Practical aspects; magnitude of the backward bifurcation
Omit treatment of Active TB, retain average sojourn time

- Consider system which does not explicitly include treatment of Active TB
  - BB is local behavior near DFE

- Retain connection to country-specific treatment data via average sojourn time

\[
D = \frac{1}{\gamma + \mu + \mu_T} = \frac{\gamma_1 - \gamma_1 ds + \mu + d\gamma_2 + d/2 + d\mu_T}{(\mu + \mu_T + \gamma_2 + ds/2)\gamma_1 + \mu(d/2 + \mu + \mu_T + \gamma_2)}
\]
How to prove backward bifurcation

✧ Idea: Transform to a simple system that has the same bifurcation

1. Rewrite our system as $\frac{dx}{dt} = f(x, \beta)$.

2. Linearize around the DFE at $R_0 = 1$.
   
   \[ J = D_x f(x^*, \beta^*) = \left( \frac{\partial f_i}{\partial x_j} (x^*, \beta^*) \right), \]

   WLOG assume $x^* = \beta^* = 0$.

   Zero is a simple eigenvalue of $J$ with right and left eigenvectors $w$ and $v$, respectively, and all other eigenvalues have negative real parts.

3. Center Manifold Theorem.

   \[ W^c = \{ c(t)w + h(c, \beta) : c < \delta, c(0) = 0, h(c, \beta) = Dh(c, \beta) = 0 \} \]

   where $c(t) \in \mathcal{E}^c$ and $h(c, \beta) \in \mathcal{E}^s$. Only need to consider dynamics on $W^c$.

4. Center manifold is invariant under the dynamics of $\frac{dx}{dt} = f(x, \beta)$, so we have that $\frac{d}{dt} (c(t)w + h(c, \beta)) = f(c(t)w + h(c, \beta), \beta)$.

   Taylor expansion for $h(c, \beta)$

5. Simplified system

   \[ \frac{dc}{dt} = \frac{a}{2} c^2 + b\beta c, \text{ where } a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}, \quad b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}. \]
How to prove backward bifurcation

$b > 0$ for biological reasons
(need $c = 0$ stable for $R_0 < 1$ and unstable for $R_0 > 1$)

$$\frac{dc}{dt} = \frac{a}{2}c^2 + b\beta c = c \left(\frac{a}{2} + b\beta c\right) = 0$$

$$\implies c = 0, \quad c = \frac{a}{-2b\beta} \quad \text{are equilibria}$$

$a < 0 \implies \text{forward bifurcation}$

$a > 0 \implies \text{backward bifurcation}$
Backward bifurcation – Model A

Theorem 1 (Model A) The reduced system with no treatment of active TB, universal vaccination and no waning of vaccine protection (i.e. \( d = \omega = 0, c = 1 \)) has a backward bifurcation at \( \beta = \beta^* \) (i.e. \( R_0 = 1 \)) if and only if

\[
(1 - q_1)^2 [\nu(1 - q_3) + \mu] [p\mu(1 - q_2) + \nu(1 - q_3)] \beta^* V^*
\]

\[
< \mu^2 p(1 - q_1)[1 - p(1 - q_2)] \beta^* V^* \theta_1 + \gamma[\nu(1 - q_3) + \mu] [p\mu + \nu(1 - q_3)] \theta_2,
\]

where

\[
V^* = \frac{\pi}{\mu} \quad \text{and} \quad \beta^* = \frac{\mu(\mu + \gamma + \mu_T)(\nu(1 - q_3) + \mu)}{\pi(1 - q_1)[\nu(1 - q_3) + p\mu(1 - q_2)]}.
\]

• Effect of increased vaccine efficacy on backward bifurcation

\[
\frac{d\theta_2}{dq_1} = -\frac{(\mu + \gamma + \mu_T)(\nu(1 - q_3) + \mu)}{\gamma [p\mu + \nu(1 - q_3)]} < 0 \quad \frac{d\theta_2}{dq_2} = -\frac{p^2 \mu^2 (\mu + \gamma + \mu_T)(\nu(1 - q_3) + \mu)}{\gamma [p\mu + \nu(1 - q_3)][p\mu(1 - q_2) + \nu(1 - q_3)]^2} \theta_1 < 0
\]

\[
\frac{d\theta_2}{dq_3} = \frac{\nu \mu (1 - q_1)(1 - p)(\mu + \gamma + \mu_T)}{\gamma (p\mu + \nu - \nu q_3)^2} - \frac{2p\mu^2 \nu(\mu + \gamma + \mu_T)(1 - p(1 - q_2)) [p\mu(1 - \frac{q_2}{2}) + \nu(1 - q_3)]}{\gamma ([p\mu + \nu(1 - q_3)][p\mu(1 - q_2) + \nu(1 - q_3)])^2} \theta_1
\]
Backward bifurcation thresholds – Model A

- Effect of increased vaccine efficacy on backward bifurcation
  - Against initial infection $\rightarrow$ BB more likely
  - Against fast progression $\rightarrow$ BB more likely
  - Against slow progression $\rightarrow$ BB more likely, unless $\theta_l$ is very small

(a) Varying the protection against initial infection, $q_1$.
(b) Varying the protection against fast progression, $q_2$.
(c) Varying the protection against exogenous reinfection, $q_3$. 
**Theorem 2 (Model B)** The reduced system with no treatment of active TB and no vaccine protection against reactivation of LTBI (i.e. $d = q_3 = 0$) has a backward bifurcation at $\beta = \beta^*$ (i.e. $R_0 = 1$) if and only if

\[
(\nu + \mu)(\mu + \omega)(p\mu + \nu r p + \nu(1 - r))\beta^* S^*
\]
\[
+ (\nu + \mu) \left[ p(1 - q_1)(1 - q_2)\mu^2 + (\omega p + (1 - q_1)\nu)\mu + \omega \nu(1 - r + rp) \right] (1 - q_1)\beta^* V^*
\]
\[
< \mu p(\mu + \omega)\left[ (1 - p)(1 - q_2) \right] (1 - q_1)\beta^* V^* \mu + (1 - p)\beta^* S^* (\mu + \nu r) \theta_1
\]
\[
+ (p\mu + \nu)(\mu + \omega)[\gamma(\nu + \mu) + (1 - p)\beta^* S^* \nu r] \theta_2,
\]

where

\[
S^* = \frac{(1 - c)\mu \pi + \omega \pi}{\mu(\mu + \omega)}, \quad V^* = \frac{c\pi}{\mu + \omega} \quad \text{and}
\]
\[
\beta^* = \frac{\mu(\mu + \gamma + \mu_T)(\mu + \omega)(\nu + \mu)}{\pi(\mu + \omega)[(1 - r + rp)\nu + p\mu] + \mu \pi c[(\mu pq_2 - p\mu - \nu)q_1 - \mu pq_2 + r \nu (1 - p)]},
\]
Backward bifurcation thresholds – Model B

\[
\frac{d\theta_2}{dr} = -\frac{(\mu + \mu_T + \gamma)^2 \nu(\nu + \mu)(1-p)}{[\nu r \mu(1-p)+\gamma(\mu p + \nu)+\nu \mu_T r(1-p)]^2} - \frac{\nu r \mu (1-p) (\mu + \mu_T + \gamma) [\gamma (\nu + \mu p) - \mu (1-p) (\mu + \mu_T)]}{(p \mu + \nu) [\nu r \mu (1-p) + \gamma (\mu p + \nu) + \nu \mu_T r(1-p)]^2} \quad \theta_1 < 0
\]

- Effect of increased detection and treatment of Latent TB
  \( \rightarrow \) BB more likely

- Effect of increased vaccine coverage depends on magnitude of \( q_1 \)
  
  \( q_1 = 0.01 < q_1^* \approx 0.057 \)
  
  \( q_1 = q_1^* \approx 0.057 \)
  
  \( q_1 = 0.35 > q_1^* \approx 0.057 \)
“Numerical” backward bifurcation thresholds for the full model

• Center manifold theory $\rightarrow$ BB occurs when

\[ a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(x^*, \phi^*) > 0 \]

\[ b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(x^*, \phi^*) > 0 \]

• Use numerical values for all model parameters (except reinfection parameters) $\rightarrow$ nice expressions for $a$ and $b$ $\rightarrow$ mathematically tractable thresholds for BB

Ex; $\theta_2 > -4.325513938\theta_1 + 9.863666263$
Thresholds for full model

\[ c = 0.90 \]

\[ \frac{1}{\omega} = 55 \]

(a) Varying the vaccine's protection against initial infection, \( q_1 \).

(b) Varying the vaccine's protection against fast progression, \( q_2 \).

(c) Varying the vaccine's protection against exogenous reinfection, \( q_3 \).

(d) Varying the proportion of LTBI that are detected and successfully treated, \( r \).

(e) Varying vaccine coverage, \( c \).

(f) Varying the average duration of the vaccine's protection, \( 1/\omega \).
Thresholds for full model

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c = 0.90 \quad 1/\omega = 55
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Similar to Model B

Similar to Model B
Thresholds for full model

- $c = 0.90$
- $1/\omega = 55$

Not Similar to Model A

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(d) Varying the proportion of LTBI that are detected and successfully treated, $r$.  
(e) Varying vaccine coverage, $c$.  
(f) Varying the average duration of the vaccine’s protection, $1/\omega$.  

Model A
- $c = 1$
- $\omega = 0$
Why not similar to Model A?

- Thresholds for different efficacy against initial infection, $q_1$, are:
  - Very sensitive to duration of vaccine protection
  - Sensitive to vaccine coverage
Why not similar to Model A?

(b) Varying the vaccine’s protection against fast progression, $q_2$.

- Thresholds for different efficacy against fast progression, $q_2$ are:
  - Very sensitive to duration of vaccine protection
Why not similar to Model A?

- Thresholds for different efficacy against slow progression, $q_3$ are:
  - Very sensitive to duration of vaccine protection.
Metrics for magnitude of a backward bifurcation

- $R_0^*$, the eradication threshold, which specifies the degree to which the reproductive number must be reduced to guarantee disease eradication

- $P^*$, the endemic disease prevalence at $R_0 = 1$, which specifies the size of the jump discontinuity in endemic prevalence as $R_0$ crosses 1 from below
Magnitude of backward bifurcation

$R_0^*$

- (a) Baseline parameters (Table 1).
- (b) Increased detection and treatment of LTBI ($r = 0.65$).
- (c) Increased vaccine coverage and no waning of protection ($c = 0.98$, $\omega = 0$).

$P^*$

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Conclusions

• Backward bifurcation (BB) is unlikely.
  – Any possible backward bifurcation would be “small”

• BB is *caused* by re-infection, but…
  • Factors which make BB significantly more likely:
    – Increased vaccine coverage with effective vaccine
    – Increased detection and treatment of Latent TB
    ★ Factors with greatest potential to eliminate TB!

• Modeling papers can give the wrong message.
  • Backward bifurcation is *not* an argument against these interventions!
  • Benefits greatly outweigh any possible adverse effect of BB

• Exponentially distributed duration of vaccine protection is important in
  the likelihood of BB
Feng et al., Theor Popul Biol (2000)

• Backward bifurcation can occur for more biologically feasible levels of re-infection

\[ \hat{\theta}_1 > 0.30 \text{ assuming } \hat{\theta}_2 = 1 \text{ and } \hat{\mu}_T = 0 \]

• Their assumption
  all exogenous re-infections move directly to the actively infected class

• Current model
  issue of fast/slow progression still applies

\[ \hat{\theta}_1 = p\theta_1 = (0.05)\theta_1 \]

Their \( \hat{\theta}_1 = 0.30 \) is equivalent to \( \theta_1 = 6 \) in current model
Can exhibit BB

Can NOT exhibit BB

- recovery and subsequent re-infection after recovery drive backward bifurcation rather than imperfect vaccine
Comparison of mass action and standard incidence formulations

Figure D4: Comparison of thresholds for the existence of backward bifurcation from the full model in (1) and those for a standard incidence version of the full model (thin black lines). Backward bifurcation occurs for points above/to the right of the line. Baseline model parameters from Table 1 are used with two exceptions: $c = 0.90$ and $1/\omega = 55$. 
Mean sojourn time from $R_0$

$$R_0 = \beta(A + B)$$

where

$$A = \frac{\pi [(1-r+rp)\nu+p\mu]}{\mu(\mu+\mu_T+\gamma)(\mu+\nu)}$$

$$B = \frac{c\pi \left[(\mu+\nu)(-p\mu+\mu pq_2+\nu q_3-\nu)q_1+\nu(p-1)(\mu+r\nu)q_3-(\mu+\nu)(\mu pq_2+r\nu(p-1))\right]}{(\mu+\omega)(\mu+\nu)(\mu+\mu_T+\gamma)(\nu-q_3\nu+\mu)}$$

- if all infections immediately become active TB ($p=1$)
- noting that vaccination doesn’t affect mean sojourn time ($c=0$)

$$R_0\big|_{p=1, c=0} = \frac{\beta\pi(\gamma_1 - \gamma_1 ds + \mu + d\gamma_2 + d/2 + d\mu_T)}{\mu[(\mu + \mu_T + \gamma_2 + ds/2)\gamma_1 + \mu(d/2 + \mu + \mu_T + \gamma_2)]}$$
Should everyone be vaccinated with BCG?

[Map showing BCG recommendation types worldwide]

http://www.bcgatlas.org

Zwerling, et al. (2011). PLoS Medicine, 8(3)
Can we establish conditions which justify the discontinuation of mass BCG vaccination?
Original Results


- Unlikely that LTBI treatment would outperform mass vaccination

Even if treating 35% of LTBI, vaccine efficacies have to be very low to justify discontinuation of mass vaccination.
Original Results


- WHO TB database to parameterize for 8 countries
- *How much better? & cost-effectiveness*
- LTBI treatment *never* outperforms mass vaccination

\[ q = 1 - (1 - q_1)(1 - q_2)(1 - q_3) \]

**horizontal axes:** overall protective effect

**vertical axes:** cumulative proportion of active TB cases prevented over 50 years

\[ 0.10 < r < 0.40 \]

\[ 0.00 < r < 0.30 \]
Original Results


- Vaccine is 1-2 orders of magnitude less “cost-effective” in low incidence setting.
- Re-infection (both exogenous and after recovery) is very important in making a vaccination decision.
- The interference of BCG with detecting latent TB is NOT.

Table 1: Vaccinations per case of active TB prevented after 50 years

<table>
<thead>
<tr>
<th>Country</th>
<th>5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
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