Modeling of the tuberculosis spreading and analysis of factors influencing the epidemic process

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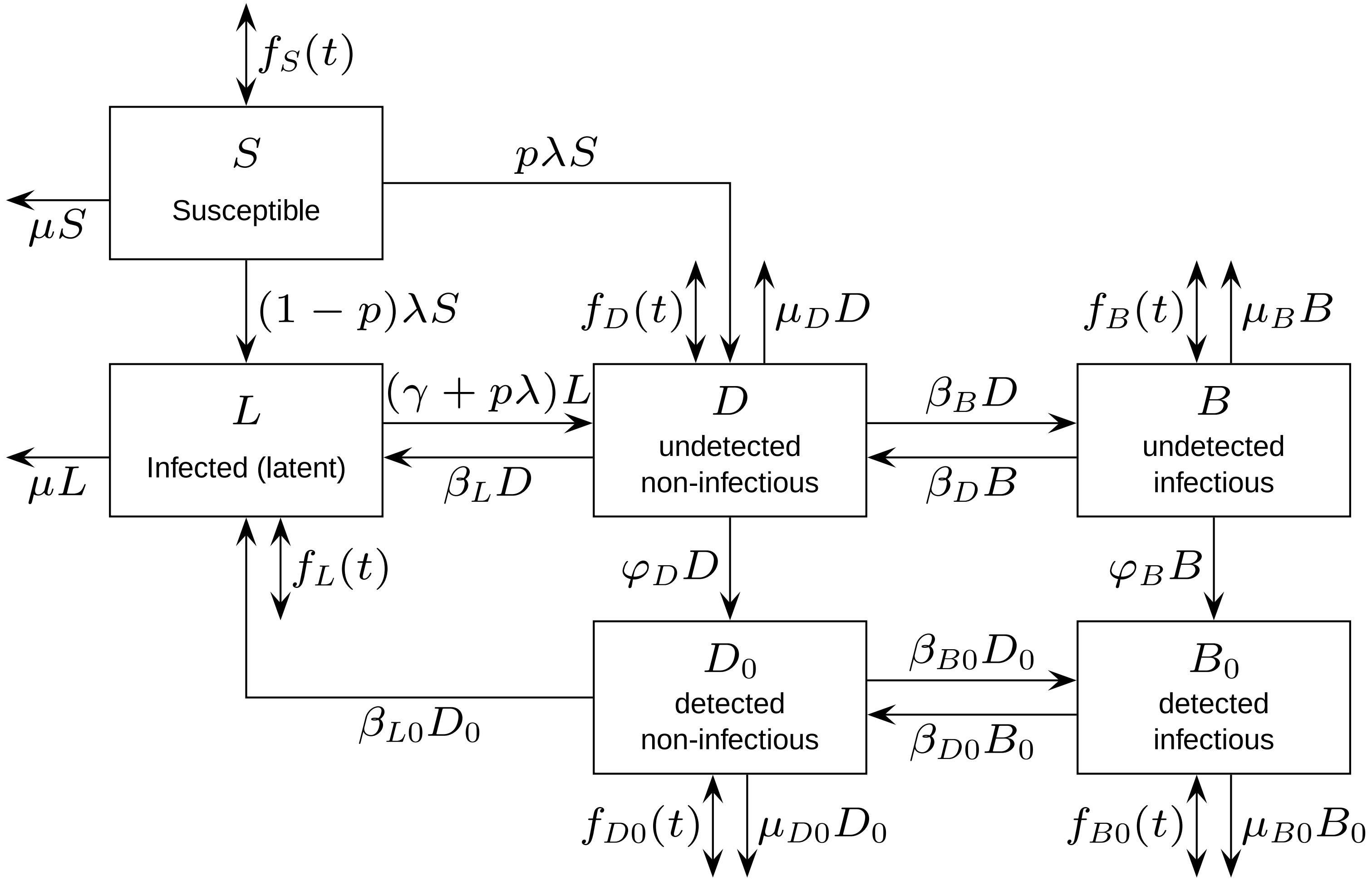
Goals of modeling in TB epidemiology

* **Traditional:** analysis of factors and variables determining the basic reproduction rate R_0 and, thus, conditions of disease elimination.

* **We suggest a new way of models' application:** estimation of the prevalence of undetected TB cases and an attempt to quantify the influence of external factors on the epidemics process.

Mathematical model



Perelman M.I., Marchuk G.I. et al. *Tuberculosis epidemiology in Russia: the mathematical model and data analysis* // Russ. J. Numer. Anal. Math. Modelling. 2004. Vol.19. No.4. P.305-314.

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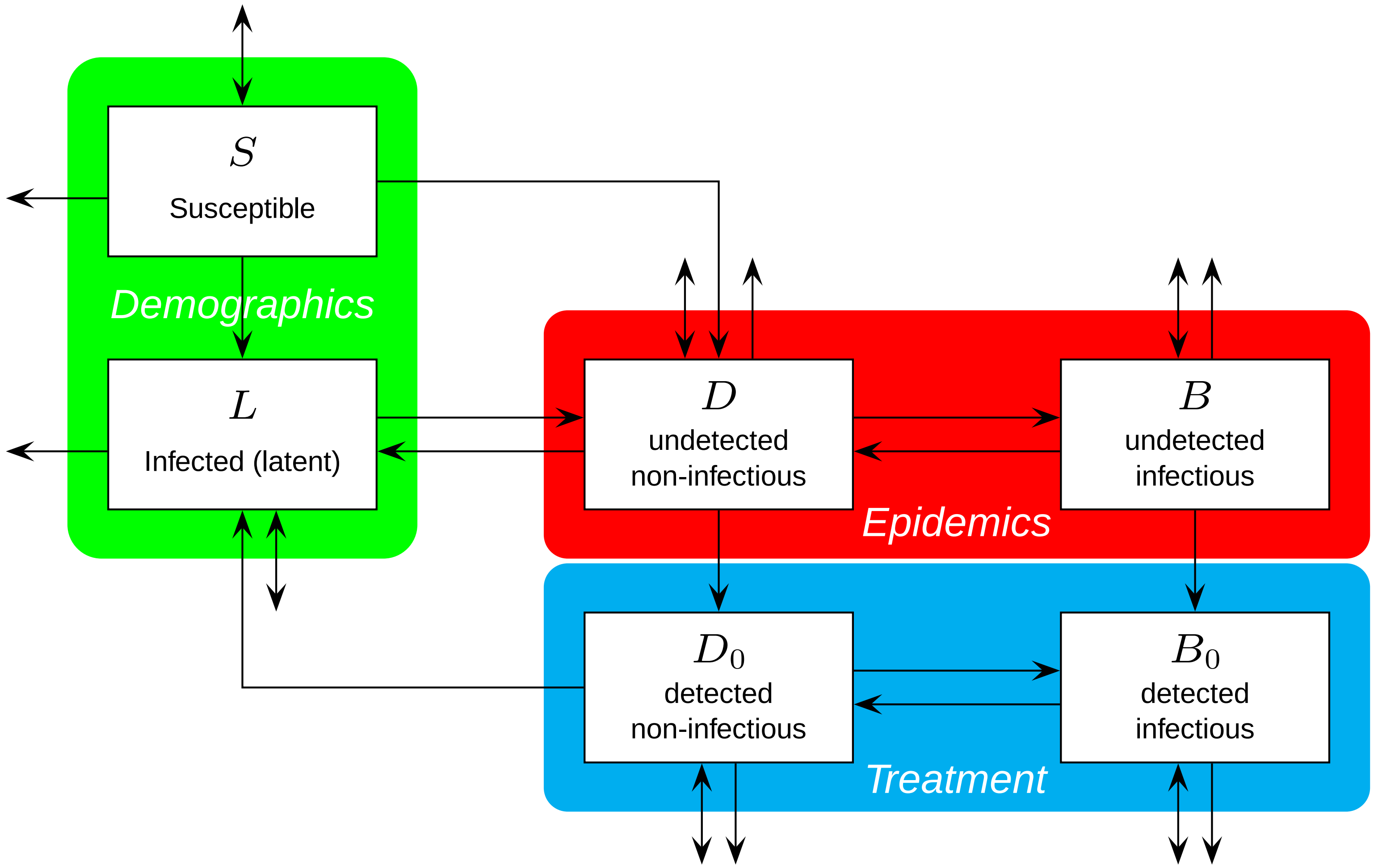

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Equations of the model

$$
\begin{aligned}
\frac{dS}{dt} =& - \beta S(B + kB_0) - \mu S + f_S(t), \\
\frac{dL}{dt} =& (1-p)\beta S(B + kB_0) - L(\gamma + \alpha_D(B + kB_0)) - \mu L \\
& + \beta_L D + \beta_{L0} D_0 + f_L(t), \\
\frac{dD}{dt} =& p\beta S(B + kB_0) + L(\gamma + \alpha_D(B + kB_0)) + \beta_D B \\
& - (\beta_B + \beta_L + \varphi_D + \mu_D) D + f_D(t), \\
\frac{dB}{dt} =& \beta_B D - (\beta_D + \varphi_B + \mu_B) B + f_B(t), \\
\frac{dD_0}{dt} =& \varphi_D D - (\beta_{B0} + \beta_{L0} + \mu_{D0}) D_0 + \beta_{D0} B_0 + f_{D0}(t), \\
\frac{dB_0}{dt} =& \varphi_B B + \beta_{B0} D_0 - (\beta_{D0} + \mu_{B0}) B_0 + f_{B0}(t).
\end{aligned}
$$

Goals

* To estimate model parameters for the regions of Central Federal District of Russia,
* To evaluate the impact of socio-economic conditions on TB in Russia.

Data

* Epidemiological data for 1998-2000 years – Database of I.M.Sechenov Research Institute of Phthisiopulmonology,
* Socio-economic data for 1998-2000 years – *Regions of Russia 2004. Statistical Digest.* Moscow, 2004

First step

Basing on results of sample investigations one can obtain the estimates of all the parameters.
We assume that:

1. Prevalence of infection and incidence of disease vary slowly over time (observational fact).

2. The regions of Russia differ in transmission coefficient β.

Given this assumptions, we obtain the following problem enabling us to evaluate transmission coefficient β, and, in turn, undetected incidence and prevalence of TB:

$$\Psi(\beta) = \left(\frac{1}{L}\frac{dL}{dt}\right)^2 + \left(\frac{1}{D}\frac{dD}{dt}\right)^2 \to \min, \quad \beta \in \left[10^{-6}, 10^{-8}\right],$$

where $\frac{dL}{dt}$ and $\frac{dD}{dt}$ are defined by the model's equations.

Results 1

Region	Prevalence of infection, L/N	Undetected pervalence of disease, $B+D$ per 100 ths.	Detected prevalence of disease, B_0+D_0 per 100 ths.
Kaluzhskaya obl.	0.52	200	242
Tul'skaya obl.	0.51	202	266
Belgorodskaya obl.	0.48	140	150
Orlovskaya obl.	0.48	193	231
Liptskaya obl.	0.46	154	241
Ryazanskaya obl.	0.46	142	247
Tambovskaya obl.	0.46	184	203
Boronezjskaya obl.	0.44	145	246
Kurskaya obl.	0.44	142	226
Ivanovskaya obl.	0.43	139	215
Tverskaya obl.	0.42	134	215
Vladimirskaya obl.	0.41	102	251
Kostromskaya obl.	0.37	107	197
Yaroslavskaya obl.	0.37	80	126

Results 2

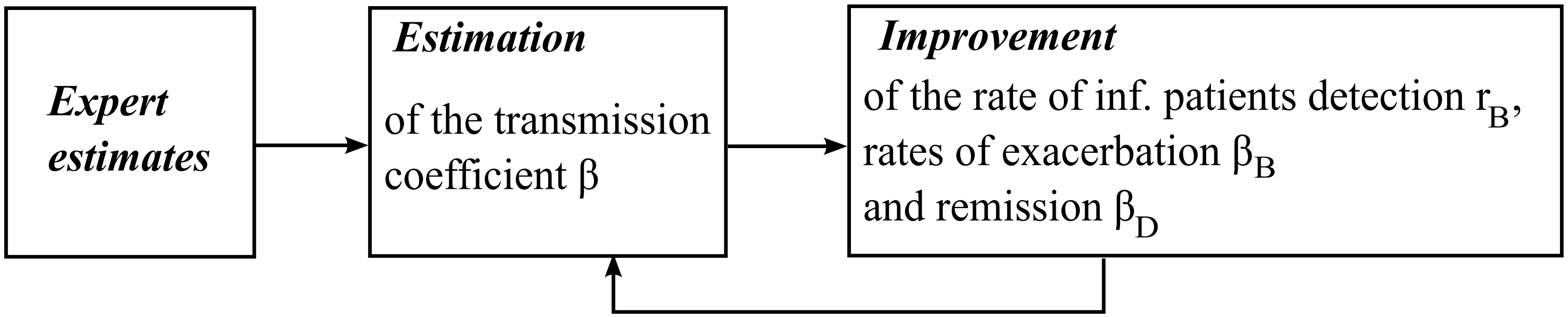
Two complications are seen in the table of estimations:

1. big spread of full prevalence of disease ($D + B + D_0 + B_0$),

2. high fraction of undetected prevalence ($D + B$) (40%-90% of detected prevalence).

We assume that the spread is caused in part by differences in other parameters besides transmission coefficient β.

Method for parameters estimation



Estimation of the transmission coef.

The sizes of groups S, L, D and B are constant

Improvement of parameters' estimates

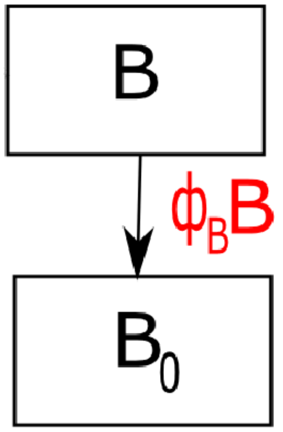
Assumption

Similarity of regional epidemiological indices

$$r_B(i) = r_B^* + \alpha_1(E_i - E_{av}),$$
$$\beta_D(i) = \beta_D^* + \alpha_2(P_i - P_{av}),$$
$$\beta_B(i) = \beta_B^* - \alpha_3(P_i - P_{av}).$$

Regional differences in health care quality

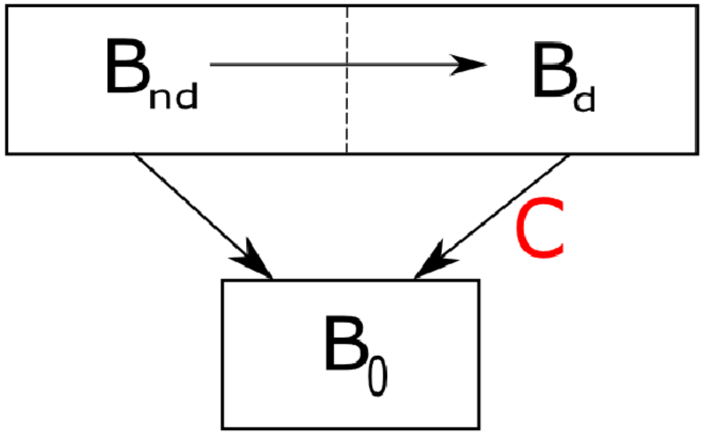
$$r_B = r_B^* + \alpha_1 \left(\frac{\phi_B B}{C} - 1.5 \right)$$



r_B – relative rate of detection of infectious patients,

$\phi_B B$ – number of newly detected infectious patients (per year),

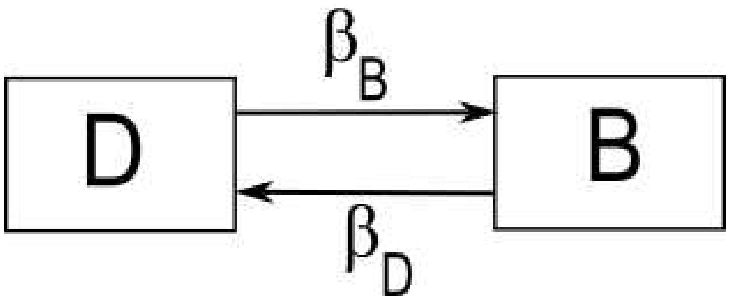
C – number of newly detected infectious patients with the destruction of the lung tissue (per year).



Regional differences in socio-economic conditions

$$
\begin{aligned}
\text{Option 1:}\quad & \beta_D = \beta_D^* + \alpha_1(\mathsf{I} - \mathsf{I}_{av}),\\
& \beta_B = \beta_B^* - \alpha_2(\mathsf{I} - \mathsf{I}_{av}),\\
\text{Option 2:}\quad & \beta_D = \beta_D^* + \alpha_1(\mathsf{H} - \mathsf{H}_{av}),\\
& \beta_B = \beta_B^* - \alpha_2(\mathsf{H} - \mathsf{H}_{av}),\\
\text{Option 3:}\quad & \beta_D = \beta_D^* - \alpha_1(\mathsf{U} - \mathsf{U}_{av}),\\
& \beta_B = \beta_B^* + \alpha_2(\mathsf{U} - \mathsf{U}_{av}),\\
& \alpha_i > 0.
\end{aligned}
$$

β_D – rate of remission,
β_B – rate of exacerbation,
I – per capita income,
H – per capita housing area,
U – unemployment level.



Impact of regional differences in socio-economic conditions and health care quality

1. Estimation of the transmission coefficient β,
2. Evaluation of the heterogeneity index $\Phi_0 = \sum_i \left(\frac{Bav - B_i}{Bav}\right)^2 + \left(\frac{Dav - D_i}{Dav}\right)^2 + \left(\frac{Lav - L_i}{Lav}\right)^2$,
3. Improvement of the estimates of parameters β_B, β_D r_B taking into account:

(a) differences in socio-economic conditions

$$\beta_D = \beta_D^* + \alpha_1(\mathsf{H} - \mathsf{H}_{av}) - \alpha_2(\mathsf{U} - \mathsf{U}_{av}),$$
$$\beta_B = \beta_B^* - \alpha_3(\mathsf{H} - \mathsf{H}_{av}) + \alpha_4(\mathsf{U} - \mathsf{U}_{av}),$$

(b) differences in socio-economic conditions and health care quality

$$r_B = r_B^* + \alpha_5 \left(\frac{\phi_B B}{C} - 1.5\right),$$

$$\Delta\Phi_a = \frac{\Phi_0 - \Phi_a}{\Phi_0} = 3.6\%, \qquad \Delta\Phi_b = \frac{\Phi_0 - \Phi_b}{\Phi_0} = 15.8\%.$$

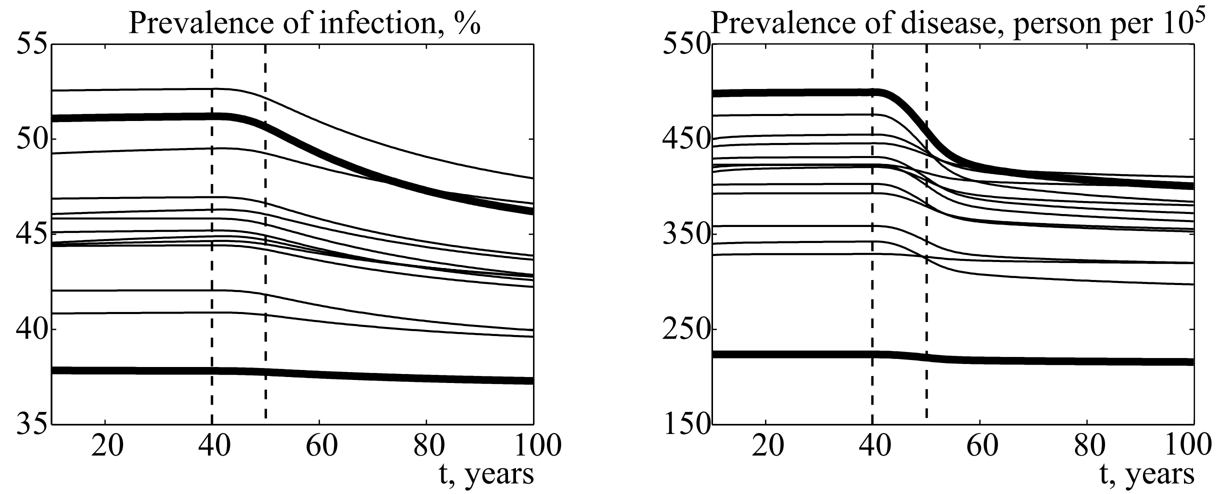
The change in the heterogeneity index Φ as a result of taking account of additional characteristics

Parameter	***Factor***	***Contribution*** (%)	
		14 regs.	***8 regs.***
r_B	FPD	10.3	51.3
r_B, β_B and β_D	FPD, income	10.9 (0.3)	51.3 (5.7)
r_B, β_B and β_D	FPD, unemployment	13.3 (0.2)	54.3 (0)
r_B, β_B and β_D	FPD, housing	13.3 (3.6)	59.6 (16.2)
r_B, β_B and β_D	FPD, income, unemployment	13.3 (0.3)	54.3 (5.7)
r_B, β_B and β_D	FPD, income, housing	13.3 (3.6)	59.6 (21.9)
r_B, β_B and β_D	FPD, housing, unemployment	15.8 (3.6)	61.9 (16.2)

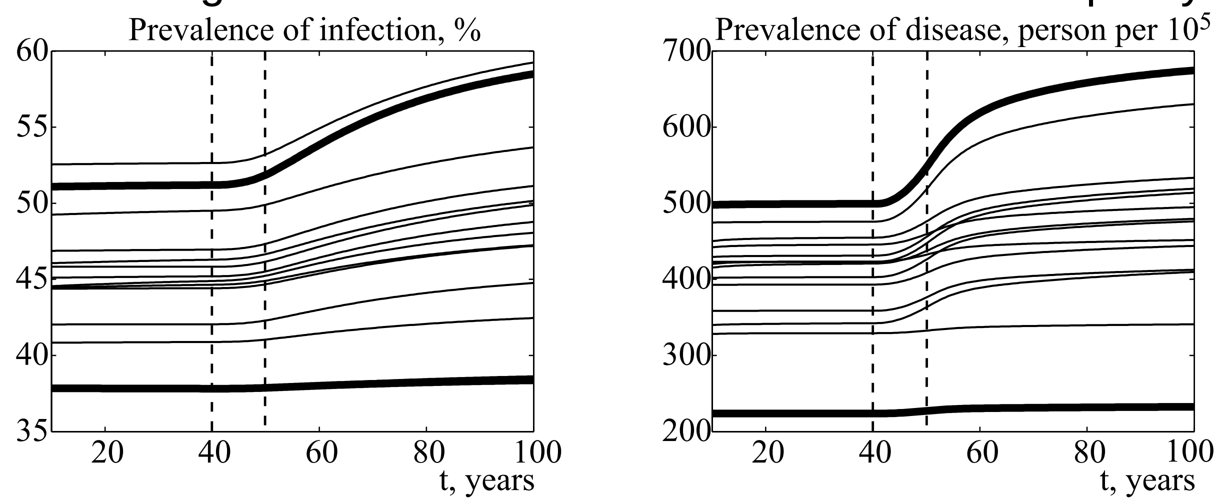
FPD – fraction of patients with the destruction of the lung tissue.

Dynamics of prevalence of disease and infection under a change in the quality of health care

Modelling the effects of improvement of health care quality

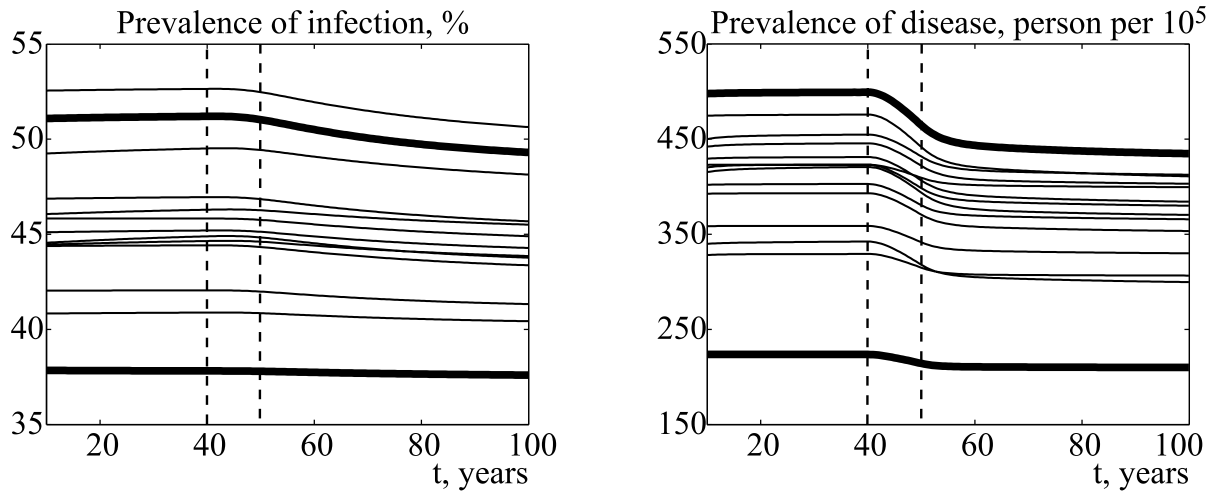


Modelling the effects of deterioration of health care quality

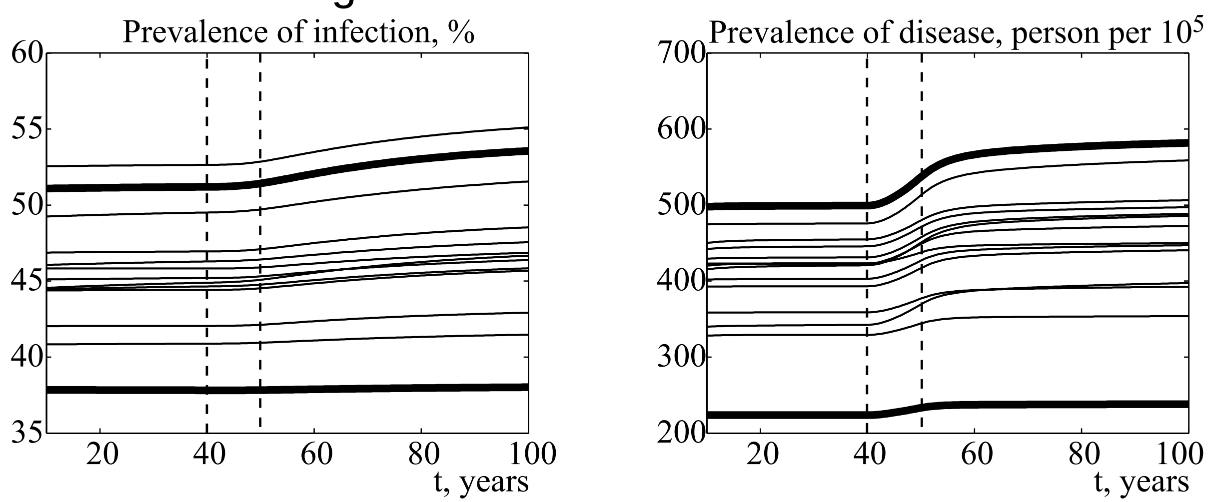


Dynamics of prevalence of disease and infection under a change of economic situation

Modelling the effects of an economic rise



Modelling the effects of an economic decline



Sensitivity analysis

	Tula (the most var.)		Yaroslavl' (the least var.)	
Prevalence of infection	I_c	4.6%	I_c	6.5%
	β	4.1%	μ	–1.7%
Prevalence of disease	γ	9.1%	γ	8.5%
	β	8.2%	I_c	5.4%

β – the transmission coefficient
γ – the rate of endogenous activation
μ – the rate of natural mortality
I_c – the fraction of the infected individuals among young people

Conclusion:

2 distinct modes of TB persistence are observed:
Yaroslavl' region – the endogenous activation of infection among people who were infected in childhood.
Tula region – the endogenous activation and the exogenous infection.

Problems

The analysis of real date revealed the limitations of the approach used:

1. Homogeneity problem:

- $\ast$ assumption of global mixing of a region's population distorts the real scheme of infection spreading,
- $\ast$ assumption of uniformity of cohorts S, L, D, and B does not account for social, age, sexual, and other differences across individuals.

2. Parameters constancy problem:

- $\ast$ apparently, properties of the infection and the individuals change with time.

An attempt to take account of the details in traditional compartmental or cohort models results in the model dimension problem: the models become too large and inconvenient for analysis.

Future investigations

Individual-based models of varying complexity can be used to solve the problems. The models shuould take account of the individuals' differences in resistiveness, chance of being infected and detected, effectiveness of treatment and in other properties.

Individual-based approach enables one to account explicitly for dependence of state of infection on individual biological and socio-economical properties.