The effect of behavioral change on tuberculosis epidemics: modeling helminthes loads and tuberculosis dynamics

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Abstract

Tuberculosis is a common and deadly disease that annually causes about two million deaths, mainly in developing countries. It is believed that the ineffectiveness of tuberculosis vaccines can be attributed to the presence of intestinal parasites and that campaigns to protect people from tuberculosis will fail in areas with endemic helminth infestation. Reducing helminth loads requires a combined intervention involving altered individual behavior—improved hygiene practices—and collective action—sanitation infrastructure. Traditionally the focus of tuberculosis research is on treatment, which will remain unsuccessful if it does not address behavioral and collective action problems.

Based on a traditional epidemic model of tuberculosis within a networked population of agents, we introduce factors that affect helminth loads. Agents with helminthes have increased probability to derive the active stage of tuberculosis and are more likely to die from the disease. Public health infrastructure improvements can reduce the environmental occurrence of helminthes, and improved individual hygiene (e.g. hand washing and wearing of shoes) reduces the infection rates of tuberculosis and helminthes. In order to identify trade-offs between solving public-health collective action problems (*public health and prevention* or group level behavioral changes) vs. failing to solve those problems (*medical treatment* or individual reliance of treatment of active TB), we analyze the model for different levels of solutions to collective action problems. We show that in social networks with more long-distance interactions, which are increasingly experienced in a globalizing world, tuberculosis cannot be effectively reduced with treatment only and require a significant behavioral changes.

1. Introduction

Tuberculosis is a common and deadly disease that annually causes about two million deaths, mainly in developing countries (Dye *et al.*, 1999). It is believed that the ineffectiveness of tuberculosis vaccines can be attributed to the presence of intestinal parasites and that campaigns to protect people from tuberculosis will fail in areas with endemic helminth infestation. There is a much higher prevalence of pulmonary tuberculosis in patients with helminth parasites compared to other population groups (Tristao-Sa *et al.* 2002, Lifson *et al.* 2002), which can partly be explained by the underlying immunological responses to helminthes (Bentwich *et al.* 1999, Borkow *et al.* 2000, 2001, Cooper *et al.* 2000, Elias *et al.* 2001, 2006).

Reducing helminth loads requires a combined intervention involving improved hygiene practices and sanitation infrastructure, which can require public health regulations to solve collective action problems (Singer and Ryff, 2007). The adoption of individual hygiene behaviors is only relevant at the group level when the reproductive value (R_0) of the infection (e.g., helminthes) is less than one as a consequence of collective adoption of the new behavior. For example, if 30 percent of individuals in *a hypothetical* population begin to wash their hands regularly before and after eating, after defecating, or after touching contaminated soil or animal flesh, and Ro decreases from 8 to 0.5, then it is only necessary for 30 percent of the population to adopt these sanitary behaviors.

The impact of public health on helminthes, and subsequent impact on tuberculosis, was estimated using results of community-level programs designed to reduce rates of gastrointestinal communicable diseases (Aiello and Larson 2002, Clasen

et al. 2007, Cifuentes *et al.* 2004, Rabie and Curtis 2006). This proxy was determined appropriate because the modes of transmission of protozoa, viruses, and bacteria that cause gastrointestinal diseases is very similar to the modes of transmission of helminthes, and hence we can include the effectiveness of programs that help to eradicate gastrointestinal helminthes (Zambrano-Villa *et al.* 2002, Jimenez and Chavez 1998).

In this paper we simulate the spread of active tuberculosis disease as a function of changes in group-acquired hygiene and sanitation institutions vs. treatment among individuals diagnosed with infectious disease in communities who fail to adopt those group-level institutions. We show that group-acquired hygiene and sanitation substantially decreases the number of individuals requiring treatment for active tuberculosis.

2. Model description

2.1 General description

The model is an extension of Cohen *et al.* (2007) who developed an agent-based model of the dynamics of tuberculosis epidemics. Agents are connected in a social network, and in monthly time steps agents can get infected, re-infected, relapse or recover. We extended the model by including the impact of helminth-mediated immunosuppression, affecting the rates of tuberculosis infection and progression to the tuberculosis infectious stage. Furthermore, we included group-level enforced institutions (i.e., public health interventions) that affect the behavior of groups of individuals (collective hygiene) and community-regulated public health interventions (e.g., clean

water supply, waste disposal). We first briefly summarize the original model of Cohen *et al.* (2007) before discussing our extension.

2.2 Cohen et al. model[1]

The agents are located in a network. This network is generated by first placing N agents randomly in the model space of dimensions 1x1. The agents are connected via links so that a parameterized average network density is achieved. The probability of any two agents being connected to each other is calculated so that the probability of a connection between any two agents decreases as the spatial distance between them increases. The probability that a short-length connection will be made rather than a long-distance connection is determined by a parameter, D, which represents the desired link length in the network.

Given two agents separated by distance d, the probability of a link connecting them is:

$$p = \frac{n}{2\pi D^2} e^{-Nd^2/2D^2}$$

(1)

where n is the average number of links in the network, d is the average network density, D is the desired length-scale for generating networks, and N the number of agents. When D is small, i.e. $D = 2$, agents will be preferentially connected to agents within their immediate spatial vicinity. When D is larger, i.e. $D = 10$, agents are more connected with

[1] A detailed description of the model and the software can be found at:

http://www.openabm.org/model-archive/tuberculosishelminthes.

individuals at greater distances from Ego, that is, they are more 'globally' connected (Figure 1).

[Figure 1]

Cohen *et al.* used a *modified* susceptible (S)-exposed (E)-infected (I)-recovered (R) structure consistent with prior TB models (Blower *et al.* 1996; Murray and Salomon 1998) by including latency and reactivation states. Agents exist in one of several mutually-exclusive epidemiological states (*epistate*): Susceptible to infection (S), Latently Infected (L1, L2, L3), Actively Infectious (I), and Recovered (R).

At the beginning of each time step, all living agents are checked for mortality. Infectious agents are subject to the TB-related mortality rate, all other agents are tested against the natural mortality rate (Table 1).

After the mortality phase, all susceptible agents are checked for infection transmission through their infectious neighbors. The probability of becoming infected each month from an infectious neighbor is τ, and the overall monthly probability of infection is dependent upon the total number of infectious neighbors, so an agent's probability of becoming infected each month is $1 - (1-\tau)^k$ where k is the number of infectious neighbors. If a susceptible agent becomes infected, they move into the latent Stage 1 (L1).

All Latent Stage 1 agents are monitored for the length of time they have been in the Stage 1 Latency. During this period, these agents are subject to an elevated probability, p_1, of primary progression into active infectiousness. If the agent remains in

the (L1) stage for 5 years without progressing to infection, his probability of endogenously progressing into infectiousness is reduced and he enters the (L2) *epistate*. L2-agents have a probability, p_2, of endogenous reactivation into the active infectious state (I). They are also susceptible to becoming exogenously re-infected by a new strain of TB at the same monthly probability as susceptible agents.

If an agent who has had active TB is re-infected, his probability of progressing to an 'infectious' or active tuberculosis disease state is increased by a similar probability and for the same time period, 5 years, as during the initial infection period (L1). However, the probability of exogenous re-infection progressing to the active disease state (I) is slightly reduced by the partial immunity conferred by the original infection. This re-infection state is the L3 epistate.

Infectious agents have a monthly probability of access to drug treatment, and if they do receive the treatment, there is a monthly probability that the treatment is efficacious, which results in the agent becoming recovered and symptom-free (R epistate). If treatment is not available or unsuccessful, the agent has a chance of self-recovering back to a Latent Stage 2 *epistate*. Recovered agents have a probability, λ_T, of relapsing to infection.

[Table 1]

2.3 Introducing helminthes and behavioral responses

Unlike Cohen *et al.* 2007, we incorporated other dynamics such as changes in progression of the disease and probability of infection due to changes in collective action

(CA) (e.g.: investment in public health infrastructure, sanitation), individual health beneficial behavioral and helminth-load. Helminth-load serves as a proxy indicator for causes of immunosuppression to infectious diseases.

We added additional attributes to the agents of the model. The first attribute is helminth-load which is a variable between 0 and 1. Helminth-load h will affect the probabilities of tuberculosis infection and progression to active TB disease

The second attribute is a behavioral indicator b with values between 0 and 1. If b is 0 there is no compliance to health beneficial behavior such as population-level adoption of hand-washing before and after meals, after defecating or urinating, and after contact with farm or wild animal blood or feces. If b is 1 there is 100% compliance. The impact of perfect compliance is a reduction of infectiousness by a fraction equal to b_{max}. Hand washing, for example, reduces the probability of respiratory infection by 16% (Rabie and Curtis, 2006). Additional behavior such as using face masks and avoidance of risk probe locations can increase b_{max}. We assume b_{max} equal to 0.2. The infectiousness per contact will now be affected by individual behaviors such as hand washing, which is simply formulated as

$$\tau_i = \tau(1 - b \cdot b_{max}) \tag{2}$$

In addition, the model takes into account the effect of helminth infection on progression to active tuberculosis disease, or 'infectious tuberculosis'. For example the probability p_1 to progress to infectious tuberculosis will decrease as helminth-loads decrease:

$$\tilde{p}_1 = p_1(1 - h_{max} \cdot (1 - h)) \qquad (3)$$

where h_{max} represents the maximum reduction of the probability of progression to active TB caused by the eradication of helminthes. The same relationship between helminth-load and other dynamics of the disease is modeled with parameters p_2, μ_{TB}, λ_r and r_S.

The helminth-load is formulated as a function of individual behavior and collective action. We assume that a combination of these two initiatives will eliminate helminthes. From Cifuentes (2004) and Clasen (2007) the estimated effect of collective action and individual behavior change in the helminth-loads is respectively 60% and 40%. This estimate was compared to measurements by Aiello and Larson (2002) to confirm their validity.

$$h = 1 - 0.6c - 0.4b \qquad (4)$$

where c is the level of collective action and b is the level of compliance to individual health beneficial behavior.

In order to estimate h_{max} we completed a literature review that allowed us to estimate the difference in risk of tuberculosis infections between low and high helminth-load regions. Those infected with helminthes are assumed to have increased susceptibility, and faster progression to tuberculosis active disease (Bentwich *et al.* 1999) than are individuals who are not infected. In Table 2 findings of Elias *et al.* (2006), and Tristao-Sa *et al.* (2002) are summarized where they report cases in which individuals

infected with helminthes were two times more likely to progress to active tuberculosis disease than were individuals free of helminthes. Therefore we assume h_{max} to equal 0.5.

[Table 2]

Results

In order to model the effect of helminth-induced immunosuppression on rates of active TB disease, all simulations involved runs over 200 year periods. This allowed us to 1) isolate the conditions necessary to reach equilibrium during the initial 100 year simulation; and 2) to generate the statistical data required for further analysis using the second 100 year phase. For each combination of parameter values, 50 simulations were performed. The population at the start of the simulation consists of 3500 agents in the susceptible state (S), 800 agents in the primary progression state (L1), 4150 agents in the endogenous reactivated state (L2), 1500 agents in the exogenous reactivated state (L3) and 50 agents in the active infectious state (I). This initial distribution approximates the equilibrium for a network with D equal to 2, and no behavioral change nor treatment ($b=c=fr_T= 0$).

According to our simulations, both group-enforced collective action solutions and individual health-enhancing behaviors significantly reduce the incidence of active TB disease. The incidence, or number of new annual cases of active TB, decreases by 56 percent when all agents comply with group-enforced CA and individual health-enhancing behaviors. In addition, group level helminth-load also declines (Figure 2).

Our simulations show that combined group-enforced collective action (CA) solutions and health-enhancing behavioral change have epidemiologically significant effects on the incidence of active TB. When we only model the effects of collective action, the incidence of TB is reduced by only 63%. If collective action and behavioral change are implemented, the TB incidence decreases in our simulations by 91%. Interestingly, this large effect on the incidence of active disease does not include the use of chemotherapeutic treatment. Not surprisingly, these results are more robust for local networks, generated when D = 2 (i.e., higher rate of contact per unit time per individual) and less robust when interactions between agents are more distant (32%, 40% and 67%). However, among the latter the effects are still biologically and epidemiologically significant (Figure 3).

[Figures 2 and 3]

We also investigated the level of treatment required to reduce the TB incidence below 30 persons per 100,000 (current level of countries like Spain and Turkey). If the network of social interactions is dominated by local interactions there is no treatment level that leads to the desired reduction if individual beneficial behavior and collective action are not *both* improved (Figure 4). The effect is even more pronounced with networks where there are more long distance connections (Figure 5). This analysis shows that a behavioral change is needed in areas with high prevalence of tuberculosis in order to reduce TB incidence to desired levels, even if treatment is available.

[Figures 4 and 5]

Conclusion

We presented an agent-based model where individuals can transmit tuberculosis via connections in a social network. The basic model of TB dynamics was based on an existing model (Cohen *et al.* 2007) and extended to include behavioral changes and collective action that can reduce helminth-loads and infection rates. Since higher helminth-loads are indicators of a faster progression of tuberculosis to the active stage, behavioral changes that reduce helminth-loads will affect the TB disease dynamics at the population level.

We find that in order to reduce tuberculosis incidence below 30 per 100,000 persons, a level found in southern European countries, we would need to combine treatment, sanitation improvements, and changes in hygiene-related behavior, such as hand washing. We show that it is not possible to reduce annual tuberculosis incidence below 30 per 100,000 without behavioral changes and that more behavioral changes are expected for more connected, more globalized, social networks.

It is important to realize that the model represents a hypothetical population. Since the data on the effect of behavioral changes are only available for a limited number of studies on different countries, they have been used to show the potential of such a model. More specifically, we assume that hygiene will affect helminth-load and infection probability, and sanitation infrastructure will affect helminth-load directly in the following ways:

1) Agents with helminthes have an increased probability of 50% to develop active tuberculosis,

2) Agents with helminthes have an increased probability of 50% to die from active tuberculosis than do individuals free of helminthes.

3) Hand washing reduces the infection rates of tuberculosis by 20% and the infection rates of helminthes by 40%.

Future work needs to concentrate to apply the model to specific TB prone areas such as the Ache, a native group of South American Indians in Paraguay who experience a tuberculosis epidemic as documented by Hurtado *et al.* (2003). Such an empirically grounded model may provide insight of behavioral interventions that can contribute to eradication of tuberculosis in areas where treatment will not be sufficient nor available at affordable costs.

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Table 1: Parameters based on the model of Cohen *et al.* (2007) and Blower *et al.* (1995).

Parameter	Description	Value
τ	Infectiousness per contact per month	0.17
μ	Natural mortality per year	0.02
μ_{TB}	Active TB disease-mortality per year	0.3
γ	Birth rate per year	0.2
r_S	Self-recovery per year	0.2
λ_r	Relapse probability after 'cure' per year	0.05
r_D	Treatment efficacy per month	0.82
z	Partial immunity (protect from progression)	0.4
p_1	Primary progression to active TB probability per year	0.03
p_2	Endogenous re-activation probability per year	0.0003
f_Γ	Fraction of population with access to treatment	0
N	Number of agents	10,000
	Average node degree	15
D	Desired length scale	2 – 10
	Initial outbreak size	50
b_{max}	Maximum reduction fraction of agents with active disease, or in an infectious state, due to changes in culturally-enforced group-level individual behaviors related to gastrointestinal disease prevention.	0.2
h_{max}	Maximum reduction of probabilities p_1, p_2, μ_{TB}, λ_r, and r_s when helminthes are eradicated.	0.5

Table 2: Effect of helminthes on the occurrence to active tuberculosis disease.

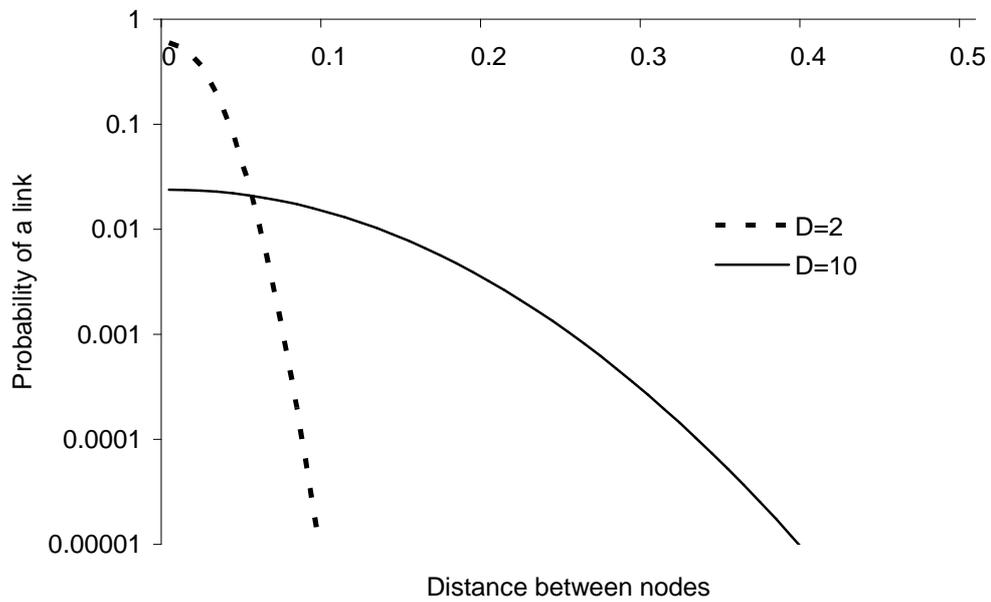|	Elias *et al.* (2006)	Tristao-Sa *et al.* (2002)
	% with Tuberculosis	% with Tuberculosis
Helminthes	71	57.8
Control	36	20.9

Figure 1: The effect of D on the network structure. With D=2 the connections are more
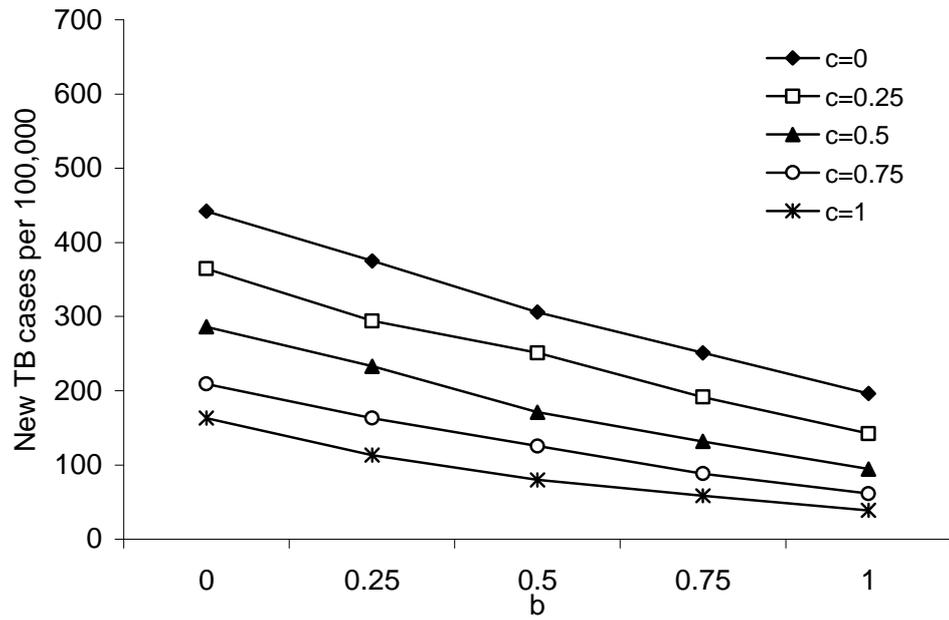
local compared to D=10.

Figure 2: TB incidence for different levels of individual health beneficial behavior (b)

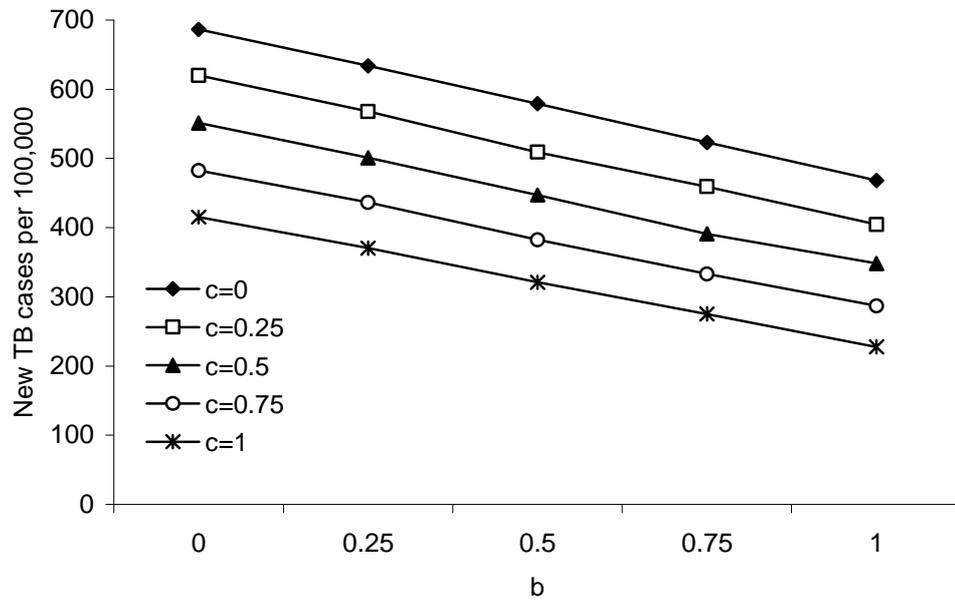and collective action (c) for networks generated with D=2.

Figure 3: TB incidence for different levels of individual health beneficial behavior (b) and collective action (c) for networks generated with D=10.
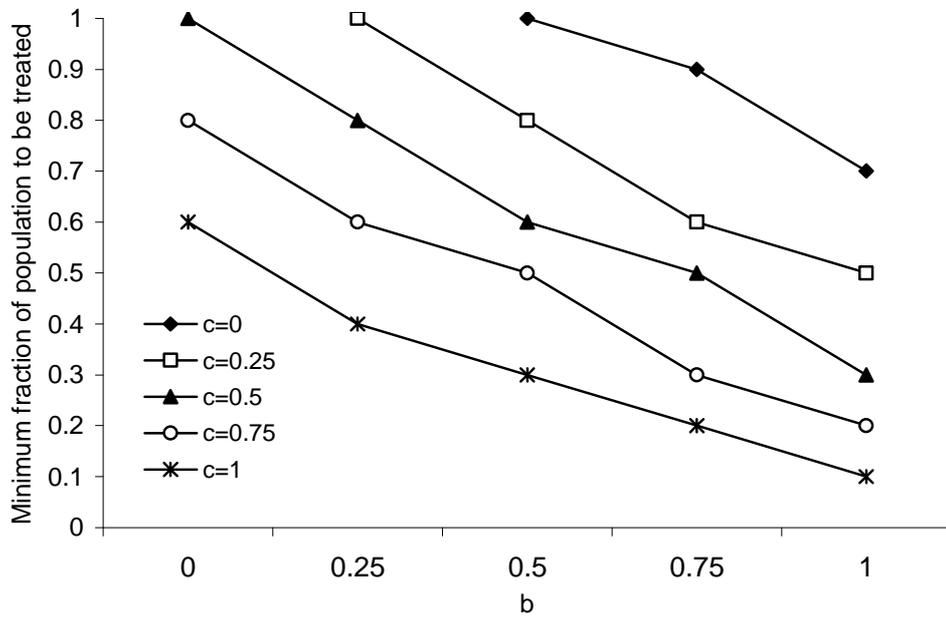
Figure 4: The minimum fraction of the population required to reach an TB incidence of 30 per 100,000 persons for different levels of individual health beneficial behavior (b) and collective action (c) for networks generated with D=2.
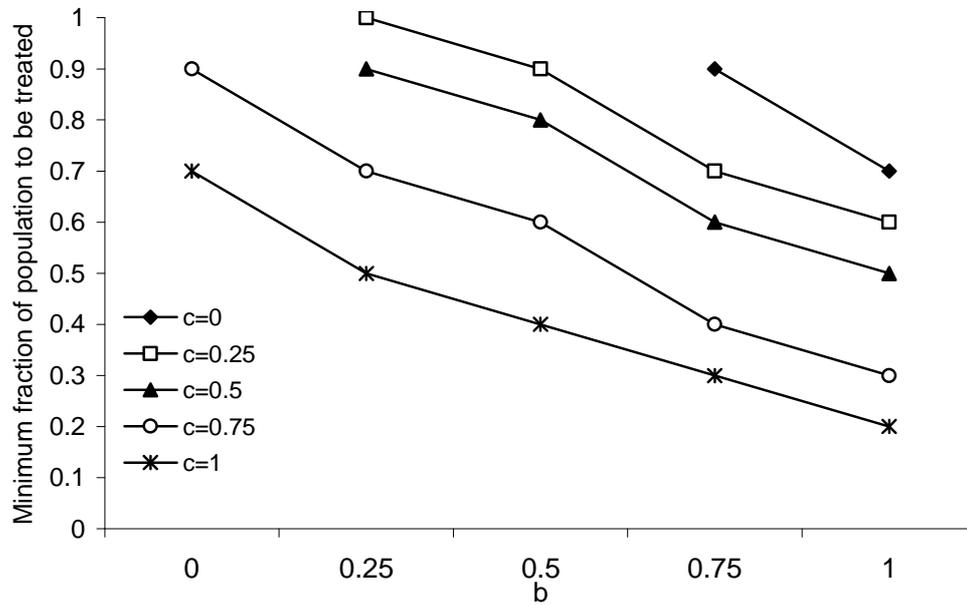
Figure 5: The minimum fraction of the population required to reach an TB incidence of 30 per 100,000 persons for different levels of individual health beneficial behavior (b) and collective action (c) for networks generated with D=10.