Tuberculosis transmission in settings of high multidrug resistant tuberculosis and explosive epidemics of HIV: A System Dynamics approach

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Introduction

Alarming rises in the incidence of tuberculosis, MDRTB, and the prevalence of HIV have been reported in several settings in recent years, notably in the former Soviet Union (FSU) (Drobniewski et al 2002, Shilova and Dye 2001, UNAIDS/WHO 2000, World Health Organization 2000, Farmer et al 1998). , At present, given the immaturity of many of these HIV epidemics, there is little epidemiological linkage between the epidemics of HIV and tuberculosis. This is, however, likely to change. Populations at risk of HIV acquisition and the development of tuberculosis are similar and mix socially and institutionally. As immune function deteriorates in those co-infected the number of cases of active HIV-associated tuberculosis is likely to rise.

The outcome for individuals with MDRTB is likely to be poor. Rates of cure with standardised short-course therapy have been reported as low as five percent. (Ivanovo Oblast 1999). Resources for effective second-line drugs are limited and institutional capacity to manage MDRTB is limited (Coker el al 2003). Individuals co-infected with HIV in this setting are likely to have a very poor prognosis (Turett et al 1995).

We developed a transmission dynamic model of tuberculosis, MDRTB, and HIV to determine the possible impact of these evolving epidemics to help guide policy decisions. The context of the study was a setting typical of many regions in the FSU, with an immature yet explosive HIV epidemic affecting principally the injecting drug using population, and high rate of tuberculosis allied to high rates of MDR tuberculosis.

We simulated the impact of two different policy decisions regarding MDRTB on cumulative death rates from tuberculosis, MDRTB and AIDS. We also analysed the impact on the epidemiology of these public health challenges if assumptions about the infectiousness of MDRTB were varied.

2. Suitability of SD modelling

The selection of SD in the current study is motivated by many reasons. Tuberculosis transmission is complex involving interactions between host, environment and micro-organism. These interactions potentially result in states including susceptible, latently infected, disease and death. Disease may be infectious or non-infectious. The environment may influence the host-micro-organism interaction (through, for example access to health services that affect duration of infectiousness or adherence to treatment and development of multidrug resistant tuberculosis [MDRTB]). Moreover, other interactions with the host, such as with HIV, may influence host responses to *Mycobacterium tuberculosis* (the organism that causes tuberculosis). Individuals infected with HIV are considerably more likely to develop tuberculosis disease once infected, and more likely to die from MDRTB if they acquire these strains. These complex interactions mean that predicting outcomes under differing scenarios may be impossible or at best flawed (Diehl and Sterman 1995, Sterman 1989 a,b)

SD maps these complex interactions in the form of causal loop diagrams (CLDs), which portray the system's variables and the causal relationships linking them. The information embedded in the CLDs covers both the quantitative and qualitative aspects of the system. The response of the system to possible policies and interventions is derived through performing tests on a simulation model reflecting the CLDs structure and relationships. These tests allow the prediction of the system behaviour under different scenarios and enhance the learning about the causal relationships driving this observed behaviour (Sterman 2000, Lane and Oliva 1998, Richardson and Pugh 1981).

3. SD in health care management

Although many modelling techniques have been applied in healthcare management, it is until recently that SD has gained a prominent position among these techniques. This has been translated by a growing number of publications of SD applications in this area (See for example the System Dynamics Review special issue on health and

health care dynamics V15 (3), 1999). A review of this literature indicates that SD has been applied in three health care areas

- Disease transmission and public health risks assessment.
- Screening for disease.
- Managing waiting lists.

3.1 Disease transmission and public health risks assessment

This stream of research includes the modelling of infectious diseases and the impact of different intervention strategies to limit their spread in human populations. Given the dramatic consequences of such diseases on public health and the economic and social costs associated with them, developing effective policies to contain them while ensuring a best use of the available resources is crucial. This area of application included, for example, the modelling of HIV/AIDS infection. These models, developed over a long period of time to accommodate new knowledge about the disease, aimed to understand the transmission mechanisms (Dangerfield 1999, Dangerfield and Roberts 1994,1996,1999a, Dangerfield et al 2001). These models included variables such as AIDS incubation period, stages of the disease, availability and effectiveness of treatment, stage at which treatment starts, and survival periods. These variables were used to quantify the effects of different prevention and treatment policies such as the Highly Active Anti-Retroviral Therapy (HAART). Similarly, another study modelled the effects of intervention policies to tackle Dengue fever epidemics in Mexico (Dunham and Galvan 1999). The model portrayed the dynamics resulting from the interaction of mosquitoes, humans, transmission virus, and government intervention policies and included variables such as the size of mosquitoes' population, mosquitos' infectivity , susceptible population size, mosquito to human density ratio, human living conditions, and epidemic control techniques. The model was used to evaluate the effects of different policies and to guide decision making for the Mexican health authorities.

3.2 Disease screening

The performance of different screening policies as well as their cost-effectiveness has constituted an important area of application of SD modelling in health care. Given the importance of screening as a tool to detect a disease before it causes harm, and its impact on disease transmission mechanisms, it was important to evaluate the medical, social, and financial consequences of different screening strategies. A first model, to study the screening of cervical cancer, was developed with the aim to investigate the effects of time interval between successive screenings and the proportion of susceptible population to be covered by the screening program (Royston et al 1999). The model was built to assist the UK Department of Health to achieve its target to reduce the disease prevalence. The model offered useful insights on how the interaction between the screening variables and the disease transmission dynamics impacted the disease incidence level. It enabled the decision-makers to decide about the best screening policy. In the same context, another model was developed to investigate the cost effectiveness of Chlamydia screening programmes (Townshend and Turner 2000). It included variables related to the transmission of the disease, sexual behaviour of susceptible population, treatment effectiveness, and population groups. The model has led to useful recommendations regarding the health care and financial consequences of different screening programmes.

3.3 Modelling of waiting lists

"Waiting lists" are a "hot" political issue. It is not surprising, therefore, that the problem has attracted a great deal of SD modelling. The dynamics of waiting lists have been studied in different contexts and many models have been built to analyse variables influencing their size and length as well as the impact of policy decisions.. For example, Wolstenholme (1993,1999) studied the cause of waiting lists escalation in the context of the UK Government decision to shift elderly community care responsibility from the Department of Health to the Local Government social services. The model showed that the intended policy of saving health care budget had a counter-intuitive effect as waiting lists exploded.

In another model, Coyle (1984) examined the policy of shortening the period of hospital stay in order to reduce the waiting lists. His model demonstrated that this policy had a counter-intuitive affect as short stays increased the probability of patient relapse and readmission to hospital for treatment: inflating waiting lists.

More recently, a model of the UK national waiting list was developed (Van Ackere and Smith 1997,1999). This model related the waiting list to the availability of resources (surgeons, beds), the demand on the NHS sector, and the available capacity in the health care private sector. The model showed that the policy to shift more patients to the private health sector when NHS waiting lists become lengthy was not sustainable. The reason was that whenever waiting lists reduced, patients tended to shift back to the NHS sector increasing in the NHS waiting lists, hence the original problem.

Although these are the key areas in which SD modelling has been applied, there are other models which focused on specific health care management issues such as health care work-force planning and emergency health care provision (Royston et al 1999), effect of joint health care provision by different sectors (Wolstenholme 1999), the effect of shift from the free-to- service to self-paying service (Hirsch and Immediato 1999), and management of accident and emergency departments (Brailsford et al 2004, Lane et al 2000). These models demonstrate the rich variety of areas in which SD may play a significant role in health policy design.

4. Tuberculosis transmission feedback structures

4.1 Drug Sensitive Tuberculosis (DSTB) feedback structure

The transmission dynamics of the DSTB form of the disease (the form which can be cured by a standard first line drugs regime) is driven by the processes presented in figure 1. This structure includes many balancing and reinforcing feedback loops, which reflect the processes affecting DSTB tuberculosis transmission in a TB susceptible population. The infection stage of the disease is represented by the balancing loops B1 and B2, which represents the temporal progression of individuals

from the state of "Susceptible TB" to the state of "Latently Infected DSTB" as they get infected and then from the latter state to the state of "Disease DSTB" as some of the infected individuals progress to the DSTB disease stage of tuberculosis (Vynnycky and Fine 1999, Murray and Salomon 1998, Blower et al 1996)

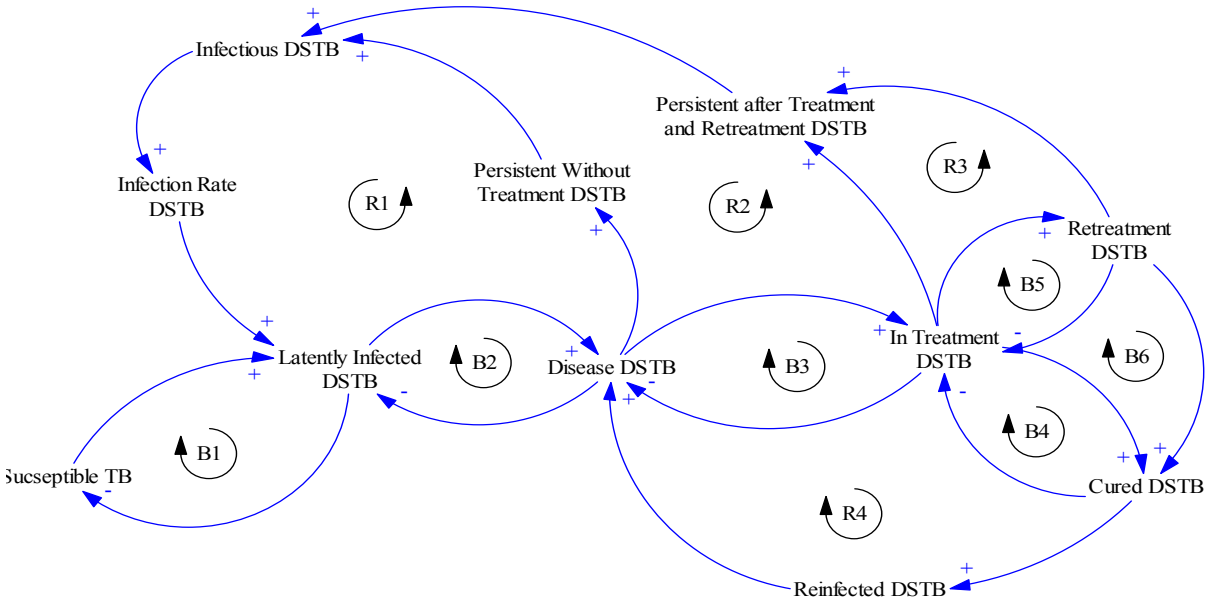

Figure 1: The DSTB transmission dynamics feedback structure

Once the individuals get to the DSTB disease stage, a fraction of these individuals is detected with the disease either through routine screening or self referral as the individual feels the disease symptoms. These individuals enter a treatment phase and move to the "In Treatment DSTB" state. If the treatment is successful, these individuals cure and progress, as a result, to the state of "Cured TB" (individuals who are not cured may die or become persistent). These processes are presented by the balancing loops B3 and B4 respectively. However, if this "first time" treatment fails, some individuals may seek treatment another time and move to the state of "Re-treatment DSTB", a process shown by the balancing loop B5.

The previous balancing processes are not the only ones in play within the DSTB transmission structure. The DSTB transmission dynamics is also affected by many self reinforcing processes, which amplify the spread of the disease. The size of the infectious population, which plays a crucial role in the disease transmission and infection rates, may change dramatically over time driven by the reinforcing processes

represented by loops R1 to R3. As individuals get infected and move to the disease state, they become infectious leading to more infected individuals among the susceptible population, which in turn, increase the size of the infectious population and so on (See reinforcing loop R1 in Figure 1). Similar processes occur when individuals fail the treatment phase and become infectious causing more infections among the susceptible population (See reinforcing loops R2 and R3 in Figure 1).

4.2 Multi-Drug Resistant Tuberculosis (MDRTB) feedback structure

In addition to the DSTB first treatment outcomes described earlier (cure, death, and persistence), some individuals may fail the treatment and develop resistance to the standard DSTB treatment based on first line drugs. In this case, these individuals develop the multi-drug resistant (MDRTB) form of the disease. The possible causes of acquiring MDRTB due to DSTB treatment failure include non-compliance with the treatment, incorrect treatment, or to natural resistance to first line drugs. This process is defined as *acquired* or *secondary* resistance.

The population developing acquired resistance has serious consequences on tuberculosis transmission dynamics. These individuals are infectious and should they infect susceptible individuals, they will transfer the MDRTB form of the disease rather than the DSTB one to the latter individuals, a process known as the *primary* infection (Pablos-Mendez et al 2002, Tahaoglou et al 2001, Dye and Williams 2000,). Therefore, the feedback structure represented in figure 1 is modified to include the processes of MDRTB acquisition and transmission as it is shown in figure 2. In this figure, the acquired or secondary infection is represented by the balancing loop B12 as some individuals entering the DSTB treatment for the first time fail this treatment episode and develop MDRTB. The MDRTB primary infection effects on the dynamic of tuberculosis are quite complex as figure 2 shows. Once the individuals who caught MDRTB through the secondary infection enter in contact with susceptible individuals, the latter then develop the MDRTB form of tuberculosis and once these individuals move to the MDRTB disease stage, they then become infectious with the MDRTB form of tuberculosis leading to more spread of this form of the disease among the population, a process portrayed by the reinforcing loop R5. Once individuals get infected with MDRTB through the primary infection process, they

move to the stage of "Latently Infected MDRTB" from which a fraction of these MDRTB latently infected individuals progress to the MDRTB stage and move to the "MDRTB" disease state. These two processes are represented in figure 2 by the balancing loops B7 and B8 respectively.

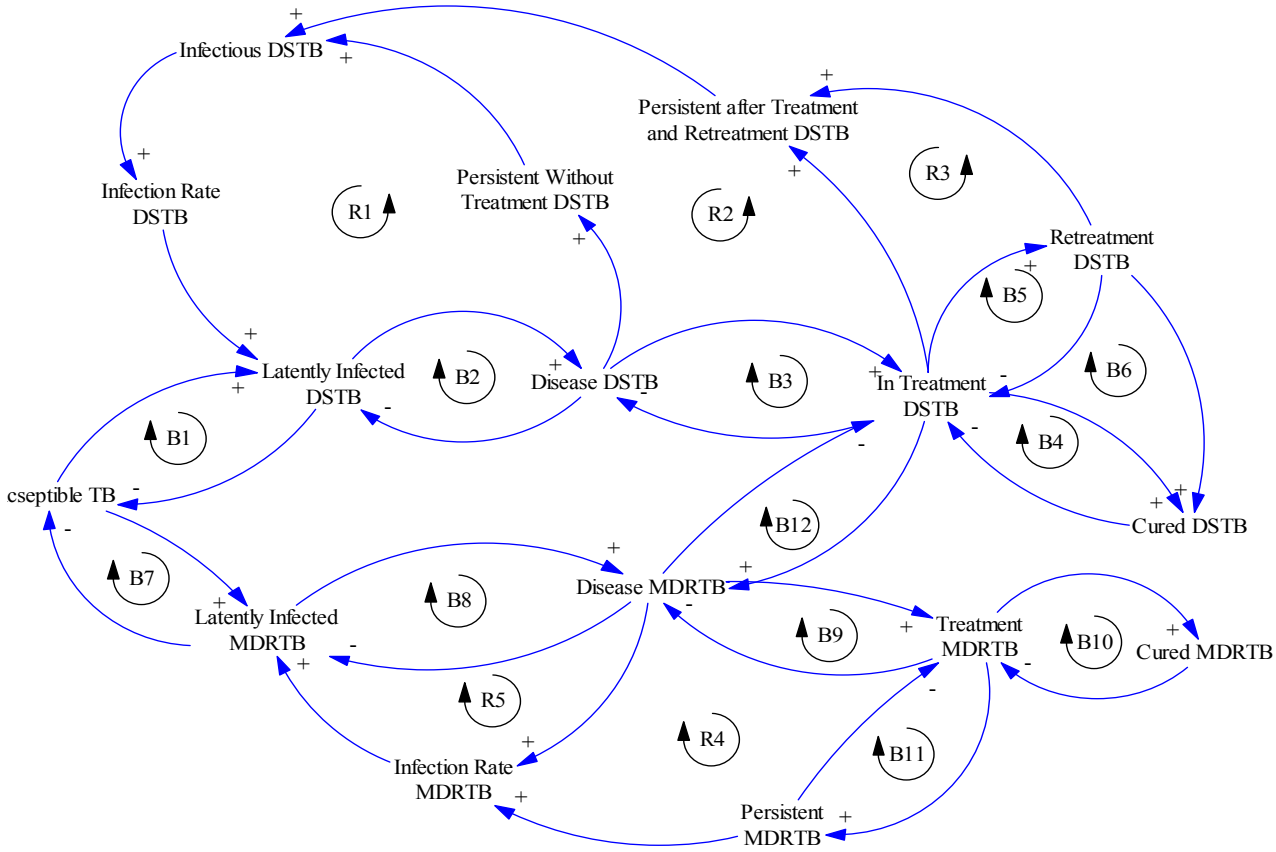

Figure 2: The MDRTB transmission dynamics feedback structure

Similarly to what was described in the DSTB case, a fraction of the individuals in the MDRTB disease state are detected and enter a special MDRTB treatment stage based on second line drugs. The outcomes of the treatment may be cure as the balancing loop B11 portrays, death, or MDRTB persistence.

The individuals in the MDRTB disease state who do not enter any treatment phase and those who become MDRTB persistent after failing the treatment phase are highly infectious and constitute the driving force behind the MDRTB spread among the tuberculosis susceptible population. As the size of this infectious population grows over time, the MDRTB infection rate increases leading to a larger MDRTB infected

population. This in turn increases the MDRTB infectious population size and, therefore, the MDRTB infection rate as the reinforcing loop R4 represents.

5. The effect of HIV on tuberculosis transmission

Although tuberculosis transmission dynamics can be affected by many factors such age, gender, living standards, and so on, there is a growing consensus among academics and decision makers that the emergence of the HIV disease has had a dramatic impact on the dynamics of tuberculosis transmission. In countries with high prevalence of HIV, the overlap between tuberculosis and HIV may exacerbate the spread of TB among the population. By reducing immunity against diseases, HIV increases the likelihood that susceptible individuals develop tuberculosis and reduces the time of progress to disease for latently infected individuals (Grassly et al 2002, Dolan et al 1998). To model the interaction between tuberculosis and HIV, it is necessary to determine the possible states of HIV disease. These states are "HIV sero-negative", "HIV sero-positive" and "AIDS". Individuals who get infected with HIV move from the state of HIV sero-negative to the state of HIV sero-positive and then to the disease state of AIDS.

To represent the effect of HIV on tuberculosis transmission dynamics, each individual is represented by two attributes: the tuberculosis state and the HIV state. It is assumed an individual moves from one HIV state to another at a rate, which is independent from the individual tuberculosis state. Therefore, individuals in any of the TB states described in the DSTB and MDRTB feedback structures move from one HIV state to another at a similar individual rate. These HIV transition rates are determined by the process of HIV infection and progress to AIDS disease (Dangerfield et al 2001, Dye et al 1998, May and Anderson 1988).

Although HIV can be transmitted through many 'routes', the model developed here is restricted to the transmission among the injected drug user (IDUs) population. This is because in settings such as the FSU, the main driver of HIV spread currently is IDUs (Rhodes et al 2002).

The feedback structure representing this process is shown in figure 3. Given the earlier assumption that transitions among HIV states are independent from the individual's tuberculosis state, an individual moving from one HIV state to another will remain in the same tuberculosis state as the HIV transition occurs. In this structure, the HIV infection rate, that is the rate at which individuals move from the "HIV sero-negative" state to the "HIV sero-positive" state as represented by the balancing loop B1, depends on the average number of drug injections per unit time, the probability that an injection is HIV infected, and the HIV infectiousness. Once an individual becomes HIV sero-positive, the transition to the "AIDS" state occurs at rate, which depends on the average AIDS transition time as it is portrayed by the balancing loop B2.

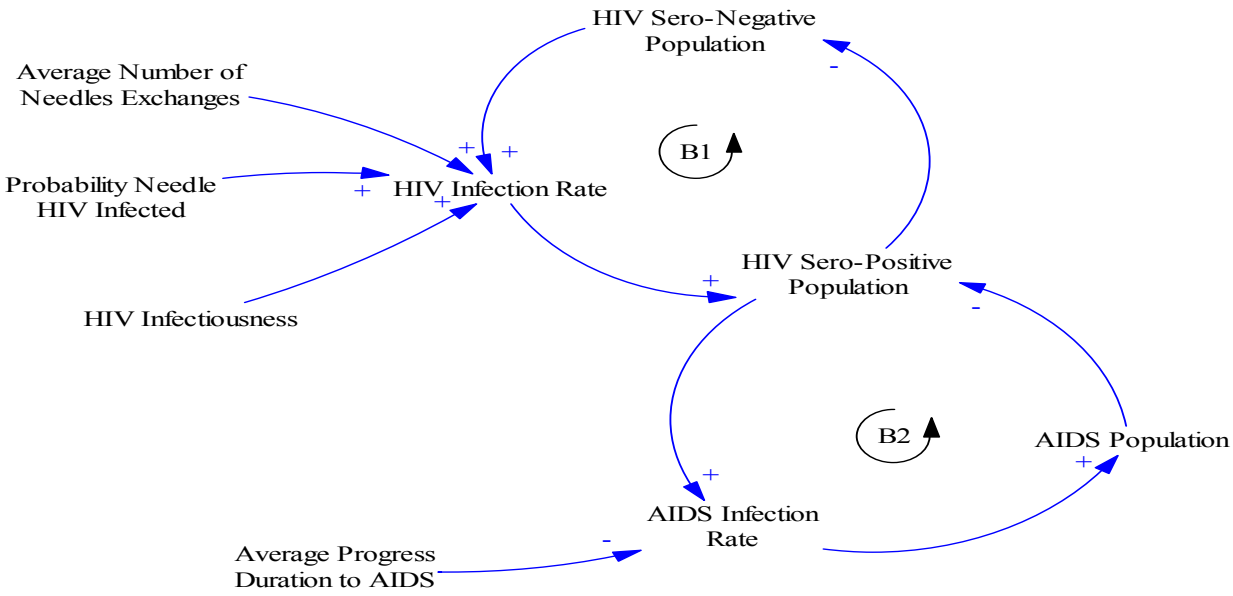

Figure 3: The HIV/AIDS transmission feedback structure

6. The System Dynamics (SD) Simulation Model

The SD model developed in the current study reflects the processes embedded in the feedback loops described earlier. It simulates the processes of tuberculosis infection and progress to disease, detection, treatment, and re-treatment of tuberculosis, primary and secondary infection with MDRTB, and MDRTB detection and treatment. The description of the simulation model is based upon the feedback structures described

earlier and include three sub-systems: the DSTB sub-system, the MDRTB sub-system, and the HIV/AIDS sub-system.

6.1 The DSTB sub-system

This sub-system simulates the processes of DSTB infection, treatment, and re-treatment portrayed in the DSTB feedback structure presented earlier (Figure 1). In this sub-system, once individuals get infected with the DSTB form of tuberculosis, they evolve through different states of infection, disease, treatment, re-treatment, cure, re-infection, and death as shown in figure 4. In the next sections, we will describe in more details the rates at which the movement among these states occur.

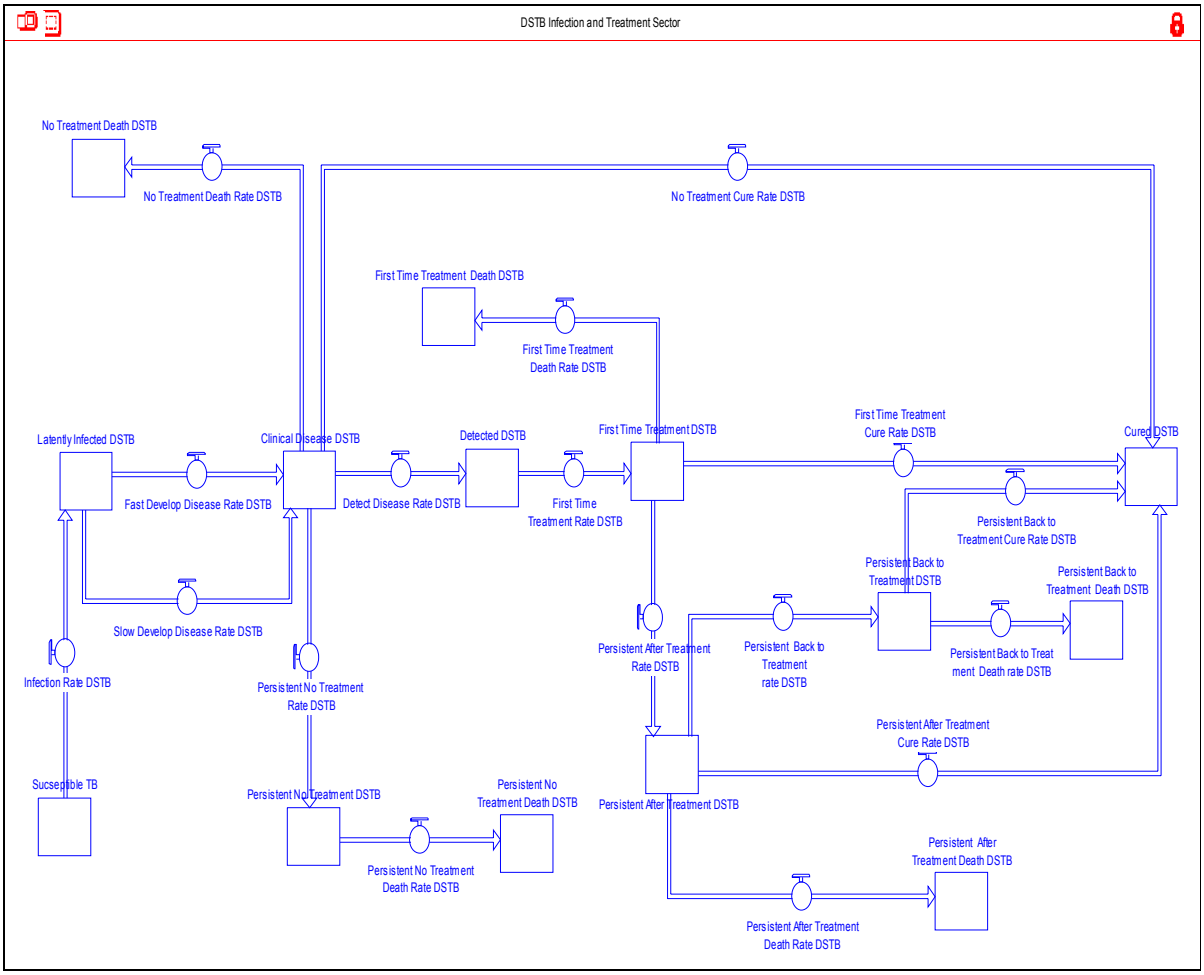

Figure 4: The DSTB stock and flow diagram

6.1.1 The DSTB infection sector

This sector, presented in figure 5, simulates the infection and progress to disease of tuberculosis susceptible individuals as they enter in contact with DSTB infectious individuals in the population. Once this infection occurred, an individual moves from the state of "Susceptible DSTB $SUSC_{TB}$" to the state of "Latently Infected DSTB $LTINFC_{DSTB}$". The latter state describes the situation in which an individual is infected but has not yet developed the disease. If this transition to disease occurs, the individual evolves from the state of "latently Infected DSTB $LTINFC_{DSTB}$" to the state of "Disease DSTB $DISE_{DSTB}$".

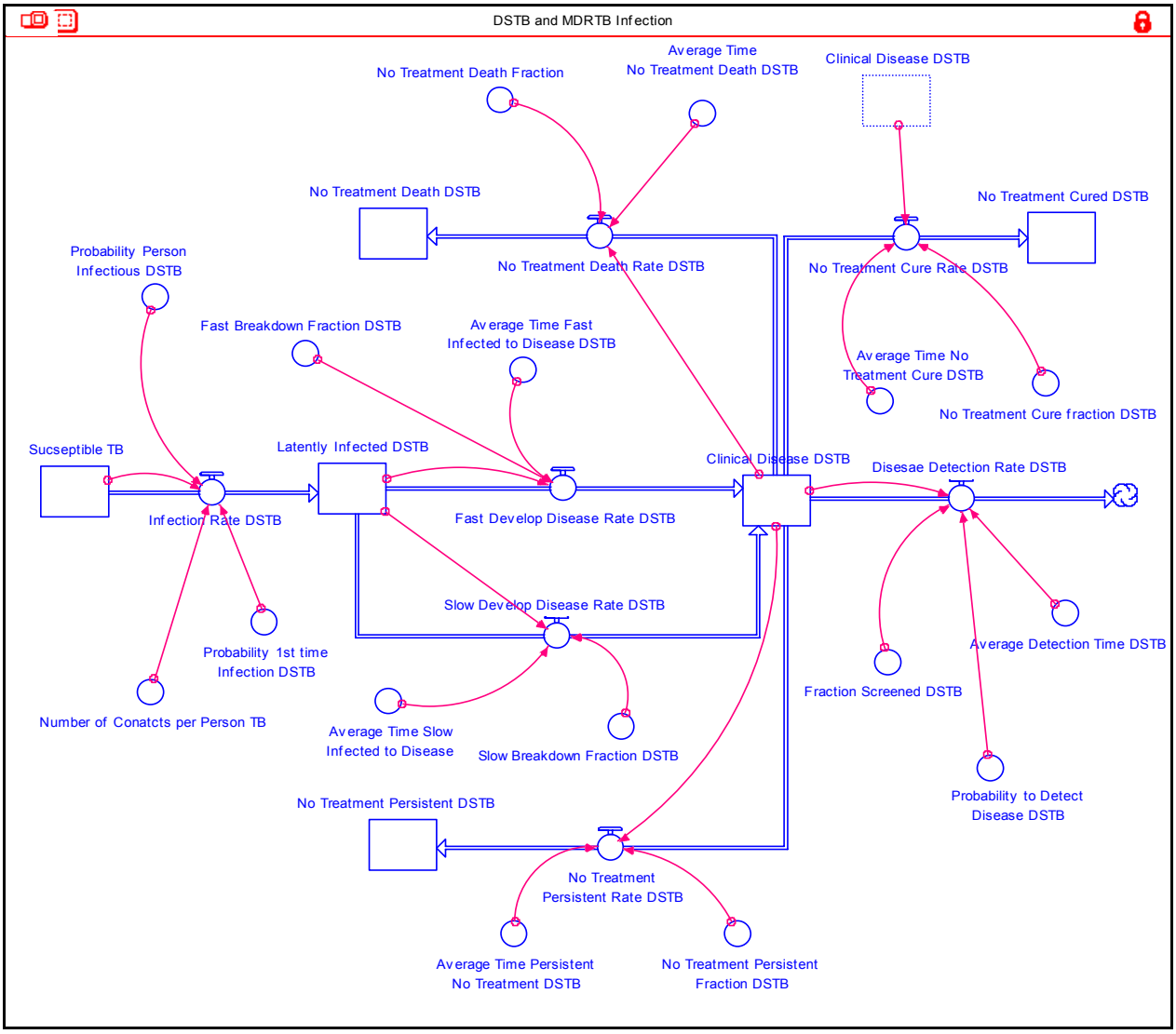

Figure 5: The DSTB Infection sector

The DSTB infection rate $INFCRT_{DSTB}$, that is the rate at which the individuals in the susceptible TB state get infected with the DSTB form of tuberculosis depends on the level of Susceptible TB stock and the individual DSTB infection risk $INFCRSK_{DSTB}$. The latter risk is driven by the average number of contacts of a susceptible individual per unit time $CTAVG_{TB}$, the probability that a contact is made with a DSTB infectious individual $PRINFCT_{DSTB}$, and the probability of DSTB transmission $PRTRNM_{DSTB}$ (infectiousness). Therefore, the DSTB infection equations are as follows

$$\frac{dSUSC_{TB}}{dt} = -INFCRT_{DSTB} \qquad (1)$$

$$INFCRT_{DSTB} = CTAVG_{TB} \times PRINFCT_{DSTB} \times PRTRNM_{DSTB} \qquad (2)$$

The rate $INFCRT_{DSTB}$ moves individuals to the stock of latently infected DSTB $LTINFC_{DSTB}$ from which they progress to the stock of DSTB disease $DISE_{DSTB}$. However, not all DSTB infected individuals get to the disease stage eventually. In fact, it is only a proportion of the infected population which progresses to the disease stage. Furthermore, there are two time frames for the breakdown to disease: fast and slow. Fast breakdown reflects a progression to disease within relatively a short period whereas slow breakdown to disease takes considerably long periods to occur. Therefore, the progress to disease is modelled through two outflows, which reflect the two mode of breakdown described earlier. The rate corresponding to each mode of disease progress depends on the infected population fraction $INFRAC_{DSTB}$ and the average transition time $LTTIMEDIS_{DSTB}$ for that mode and the level of the latently infected DSTB stock $LTINFC_{DSTB}$. Therefore, the progress to disease rates equations are as follows

$$\frac{dLTINFC_{DSTB}}{dt} = INFCRT_{DSTB} - SLOW_{DSTB} - FAST_{DSTB} \qquad (3)$$

$$SLOW_{DSTB} = \frac{LTINFC_{DSTB} \times INFRAC_{DSTB,\,SLOW}}{LTTIMEDIS_{DSTB,\,SLOW}} \qquad (4)$$

$$FAST_{DSTB} = \frac{LTINFC_{DSTB} \times INFRAC_{DSTB,\ FAST}}{LTTIMEDIS_{DSTB,\ FAST}} \quad (5)$$

If the individuals in the state of DSTB tuberculosis disease remain in this state without being detected or treated, they can evolve to three possible outcomes: death, 'self' cure, or persistent (chronic illness). The underlying variables determining these rates are the fraction of individuals $DSFRAC_{DSTB}$ and the average transition time to each outcome $DSTIME_{DSTB}$, and the DSTB disease stock level $DISE_{DSTB}$. These equations are as follows

$$\frac{dDISE_{DSTB}}{dt} = SLOW_{DSTB} + FAST_{DSTB} - NTDTH_{DSTB} - NTCUR_{DSTB} - NTPRS_{DSTB} \quad (6)$$

$$NTDTH_{DSTB} = \frac{DISE_{DSTB} \times DSFRAC_{DTHDSTB}}{DSTIME_{DTHDSTB}} \quad (7)$$

$$NTCUR_{DSTB} = \frac{DISE_{DSTB} \times DSFRAC_{CURDSTB}}{DSTIME_{CURDSTB}} \quad (8)$$

$$NTPRS_{DSTB} = \frac{DISE_{DSTB} \times DSFRAC_{PRSDSTB}}{DSTIME_{PRSDSTB}} \quad (9)$$

6.1.2 The DSTB First Treatment sector

In the previous section, we describe the outcomes associated with individuals in the DSTB disease state who remain without any treatment. However, in reality a fraction of these individuals is found to have the disease and enter, as a consequence, a treatment phase for the first time (See figure 6). Therefore, these individuals move from the stock of "Detected DSTB $DETCT_{DSTB}$" to the stock of "First Time Treatment DSTB $FSTTRM_{DSTB}$" at a rate $FSTTRMRATE_{DSTB}$, which depends on the level of the "Detected DSTB $DETCT_{DSTB}$" stock and the average time to enter the first time treatment phase $FSTTRMTIME_{DSTB}$..

The first time treatment of DSTB individuals may lead to many outcomes. If the treatment is successful, the individual is cured. If the treatment is not followed

properly, the individual becomes DSTB persistent. However, if the treatment fails, the individual dies as a consequence. In Figure 6, each of these outcomes is represented by a stock. The rates at which individuals move towards these stocks depends on the level of the "First Time Treatment DSTB $FSTTRM_{DSTB}$" stock, the fractions corresponding to each outcome, and the average transition time to each outcome.

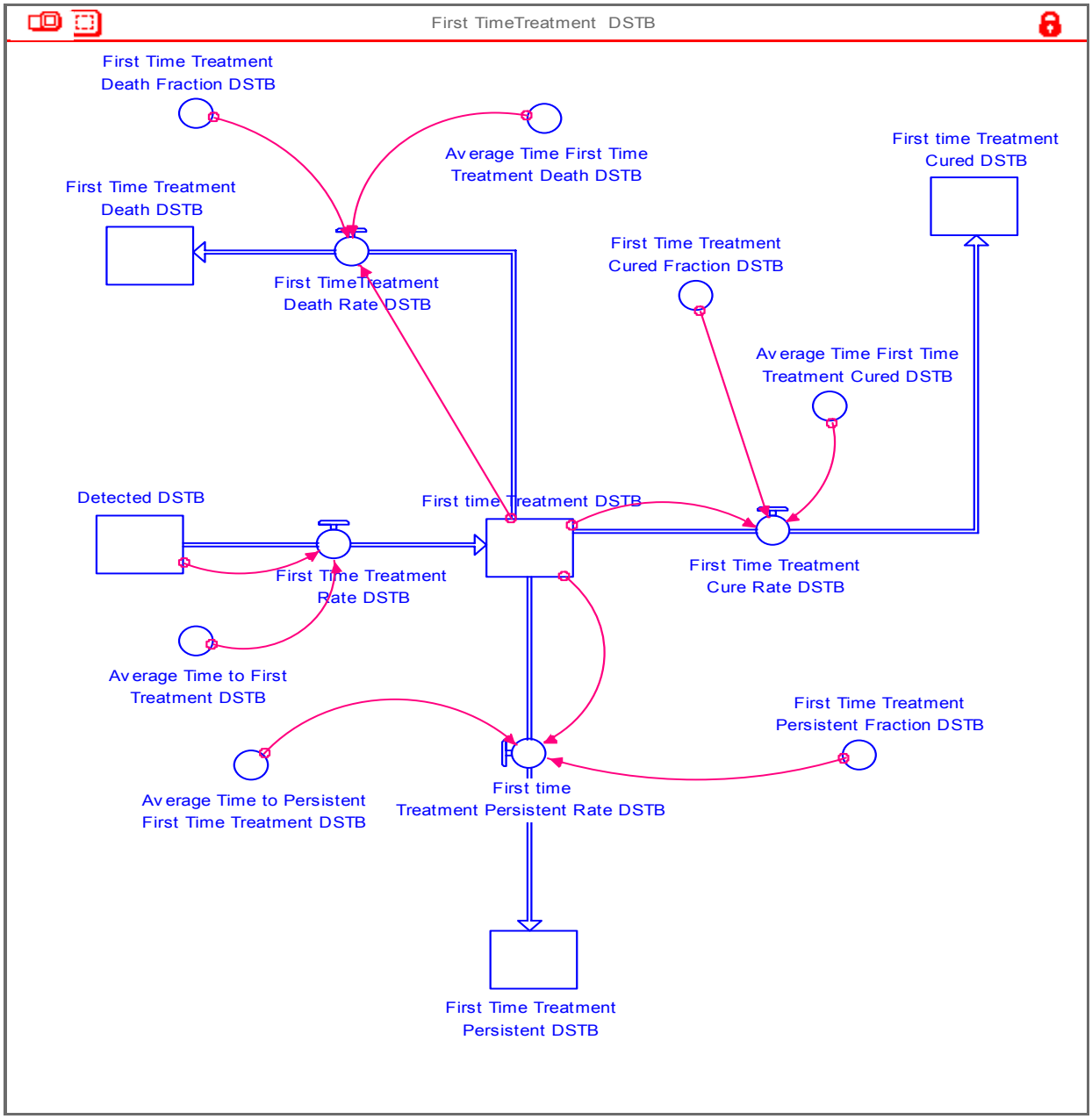

Figure 6: The DSTB first time treatment sector

The equations corresponding to the first time treatment phase outcomes are as follows

$$\frac{dFSTTRM_{DSTB}}{dt} = FSTTRMRATE_{DSTB} - FSTTRMDTH_{DSTB} - FSTTRMCUR_{DSTB} - FSTTRMPRS_{DSTB} \quad (10)$$

$$FSTTRMRATE_{DSTB} = \frac{FSTTRM_{DSTB}}{FSTTRMTIME_{DSTB}} \quad (11)$$

$$FSTTRMDTH_{DSTB} = \frac{FSTTRM_{DSTB} \times FSTTRMFRAC_{DTHDSTB}}{FSTTRMTIME_{DTHDSTB}} \quad (12)$$

$$FSTTRMCUR_{DSTB} = \frac{FSTTRM_{DSTB} \times FSTTRMFRAC_{CURDSTB}}{FSTTRMTIME_{CURDSTB}} \quad (13)$$

$$FSTTRMPRS_{DSTB} = \frac{FSTTRM_{DSTB} \times FSTTRMFRAC_{PRSDSTB}}{FSTTRMTIME_{PRSDSTB}} \quad (14)$$

6.1.3 The DSTB Re-treatment sector

Individuals becoming persistent after failing first time treatment of DSTB may die or 'self" cure after a certain period. However, these outcomes do not affect all these individuals as a fraction of them may enter another re-treatment phase as a result of established tuberculosis monitoring policies or if the individuals seek treatment as they health state deteriorate (Ser figure 7).

The outcomes associated with "persistent" individuals not entering a re-treatment phase are represented by the stocks "Persistent After First Time Treatment Cured $PRSCURE_{DSTB}$" and "Persistent After First Time Treatment Death $PRSDEATH_{DSTB}$". The rates at which the individuals move from the "Persistent After First Time Treatment $PERS_{DSTB}$" stock to the outcomes stocks mentioned above depend on the level of the $PERS_{DSTB}$ stock, and the average transition time and the fraction corresponding to each outcome (These rate equations have the same form as equations 12 and 13 above).

The individuals who enter the re-treatment phase are detected at a rate determined by the level of the $PERS_{DSTB}$ stock, the average time to detect a persistent individual, and the effectiveness of the detection procedures. Once these individuals return to treatment, they can either die or be cured. The rates at which individuals move

towards these outcomes depends on the level of the "Persistent Back to Treatment $PRSBKTR_{DSTB}$" stock, and the average transition time and the fraction corresponding to each outcome (These rate equations have the same form as equations 12 and 13 above).

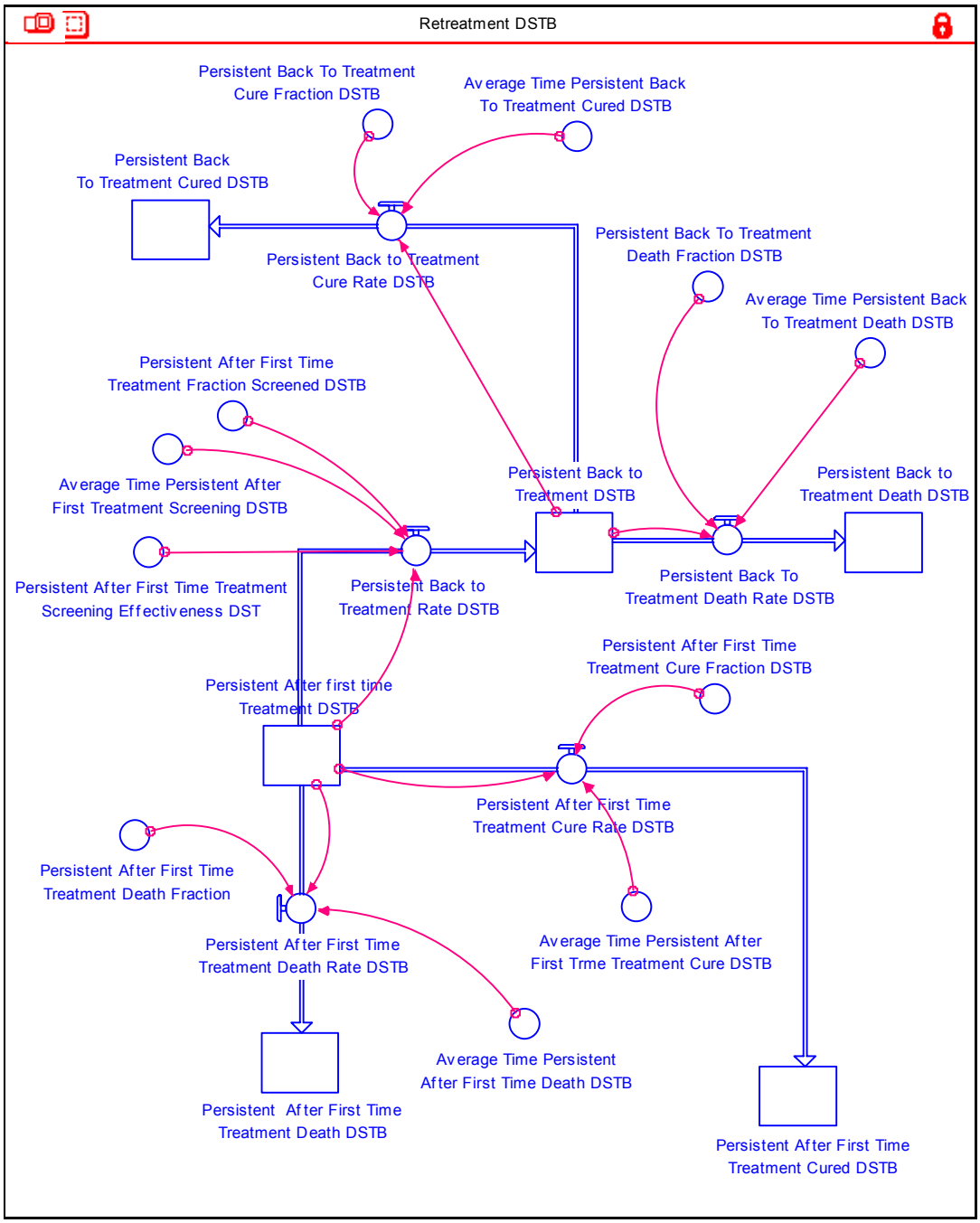

Figure 7: The DSTB Re-treatment Sector

6.2 The Multi-Drug Resistant Tuberculosis (MDRTB) Sector

In addition to the outcomes associated with the DSTB first time treatment phase described earlier (section 6.1.2), a fraction of the individuals who fail this treatment develop resistance to the drugs used in DSTB treatment. Therefore, the usual drugs used in the DSTB treatment become ineffective and no longer cure these individuals. Once individuals get to this state, they generally enter a special intensive treatment regime (based on second line drugs) from which they can either die, cure, or become persistent (See Figure 8).

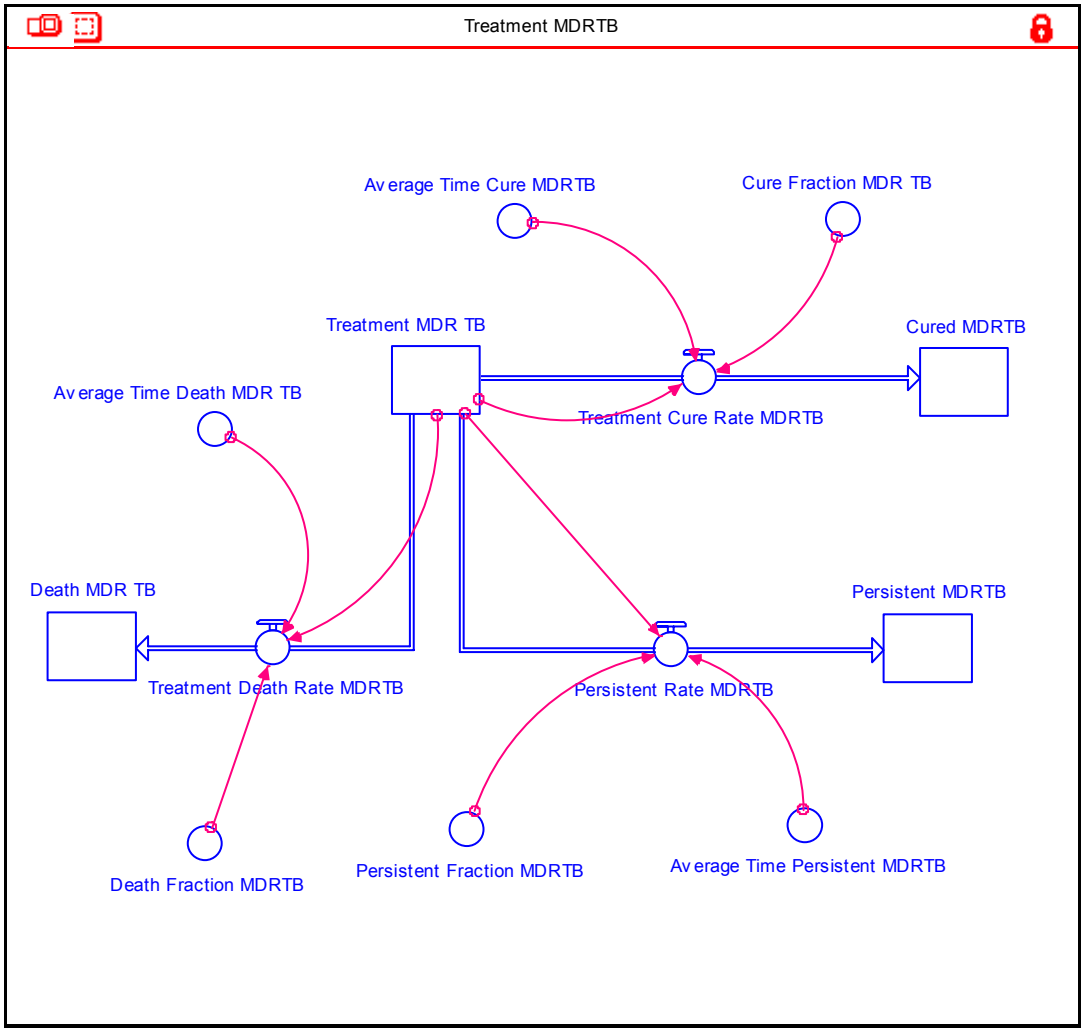

Figure 8: The MDRTB treatment sector

The rates at which these individuals move from the "MDRTB in treatment stock TRM_{MDRTB}" towards each outcome depend on the level of this stock, and the average

transition time and the fraction corresponding to each outcome (These rate equations have the same form as equations 12 and 13 above).

The individuals who develop the MDRTB form of the disease have a significant effect on the transmission dynamics of MDRTB. If they infect susceptible individuals, these individuals become latently infected with MDRTB. The rate at which this MDRTB infection occurs is determined by the level of Susceptible TB stock and the individual MDRTB infection risk $INFCRSK_{MDRTB}$, where this risk is determined by the probability that a contact is made with a MDRTB infectious individual $PRINFCT_{MDRTB}$, and the probability of MDRTB transmission $PRTRNM_{MDRTB}$ (infectiousness).

$$INFCRT_{MDRTB} = CTAVG_{TB} \times PRINFCT_{MDRTB} \times PRTRNM_{MDRTB} \qquad (15)$$

These MDRTB latently infected individuals progress to the state of MDRTB disease through fast and slow breakdown routes in a similar way as it was described earlier for the DSTB form of the disease (see equations 6 to 9). From this state they move to the MDRTB treatment phase from which the outcomes are similar to those affecting individuals who acquired MDRTB through secondary infection.

6.3 The HIV/AIDS sector

The presence of HIV/AIDS in a population may have an important effect on the tuberculosis transmission dynamics. By reducing individuals' immunity, HIV infected persons become more vulnerable to tuberculosis disease. To model the impact of HIV/AIDS in this context, it is assumed that the possible states of this disease are "HIV sero-negative", "HIV sero-positive" and "AIDS disease". Individuals in any of the tuberculosis states described earlier can also be in any of these states of HIV/AIDS simultaneously (that is tuberculosis and AIDS can overlap in the same individual). Therefore, the tuberculosis transmission model structure described earlier is replicated three times (through the Array function in the Ithink software), each structure corresponding to a particular HIV/AIDS state. In this case,

each individual can be described by two attributes: the tuberculosis state and the TB/HIV state.

Individuals infected with HIV move from the tuberculosis stock (state) in the "HIV sero-negative" $TB_{HIVNGTV}$ structure to the same tuberculosis stock (state) in the "HIV sero-positive" $TB_{HIVPSTV}$ structure (infection with HIV does not alter the individual's tuberculosis state as these are two different diseases). The rate $HIVPSV_{RATE,TB}$ at which this movement occur depends on the level of the tuberculosis stock in the "HIV sero-negative" state $TB_{HIVNGTV}$ (the state from which the individual is moving" and the individual HIV infection risk. Given that the model is restricted to HIV infection through needle exchange within the injected drug users (IDUs) population, the HIV infection risk is determined by the average number of drug injections per unit time $AVGDR_{INJ}$, the probability that the injection is HIV infected $PRINJ_{INFCT}$, the HIV infectiousness HIV_{TRANSM} (probability of HIV transmission), and the IDUs population density IDU_{DNST} (fraction of this population within the general one).

$$\frac{dTBHIV_{NGTV}}{dt} = TBHIV_{NGTV} \times AVGDR_{INJ} \times PRINJ_{INFCT} \times HIV_{TRANSM} \times IDU_{DNST} \qquad (16)$$

This equation is valid for every state describing the tuberculosis transmission dynamics.

HIV infected individuals do not remain in the "HIV sero-positive" state indefinitely as there is a progress towards the AIDS disease state. Given that this progression takes on average 10 years, the rate at which individuals move from a tuberculosis state in the "HIV sero-positive" structure to the same tuberculosis state in the "AIDS structure" is determined by the level of the tuberculosis stock in the "HIV sero-positive" structure and the average transition time between these two states (10 years). However, if an individual is in a state of DSTB and MDRTB disease or persistent and is "HIV sero-positive" at the same time, this individual moves instantaneously to the corresponding tuberculosis state in the AIDS structure.

$$\frac{dTB_{AIDS}}{dt} = \frac{TB_{AIDS}}{AVGTME_{AIDS}} \qquad (17)$$

This equation is valid for every state describing the tuberculosis transmission dynamics.

7. Scenario analysis

The model developed in this research aims to predict the consequences of MDRTB cure rate on tuberculosis deaths in contexts of high HIV prevalence. The model was calibrated on the Samara oblast, a region in south west of the Russian federation, which is witnessing an explosion in the cases of MDRTB and HIV. Two scenarios were tested using the SD simulation model. First, a cure rate of 5 percent reflecting outcomes documented from elsewhere in Russia where no second line drugs (drugs suitable to treat MDRTB) are used (Ivanovo Oblast 1999). Second, a cure rate of 80 percent is achieved representing a well resourced control program using second line drugs (Mitnick et al 2003, Tahaoglou et al 2001).

The model calibration includes two sets of parameters. First, the tuberculosis and HIV transmission parameters derived from the internationally published research. Second, the initial levels of the stock variables representing the situation in the Samara oblast at the beginning of 2003 as the model was simulated over a period of ten years from 2003 until 2012. Before presenting the simulation results, it is important that the model was validated through the structural, quantitative, and behavioural tests described in the literature. In this context, the model output replicated with high level of accuracy the behaviour over time of the tuberculosis death rate and cumulative number of deaths over the period 1997-2002.

The possible impact of MDRTB treatment effectiveness on tuberculosis transmission dynamics was analysed through the behaviour over time of the following variables under both scenarios.

7.1 Cumulative deaths from tuberculosis

This represents the cumulative number of deaths resulting from all forms of tuberculosis and includes deaths from HIV-associated tuberculosis. The outcome over time under the two scenarios is presented in figure 9. Based on this model, Samara Oblast may witness 6,303 deaths cumulatively over a ten year period from tuberculosis under scenario 1. Under scenario 2, the cumulative death rate falls to 4,465, a difference of 1,838 deaths, almost all attributable to successful treatment of MDRTB.

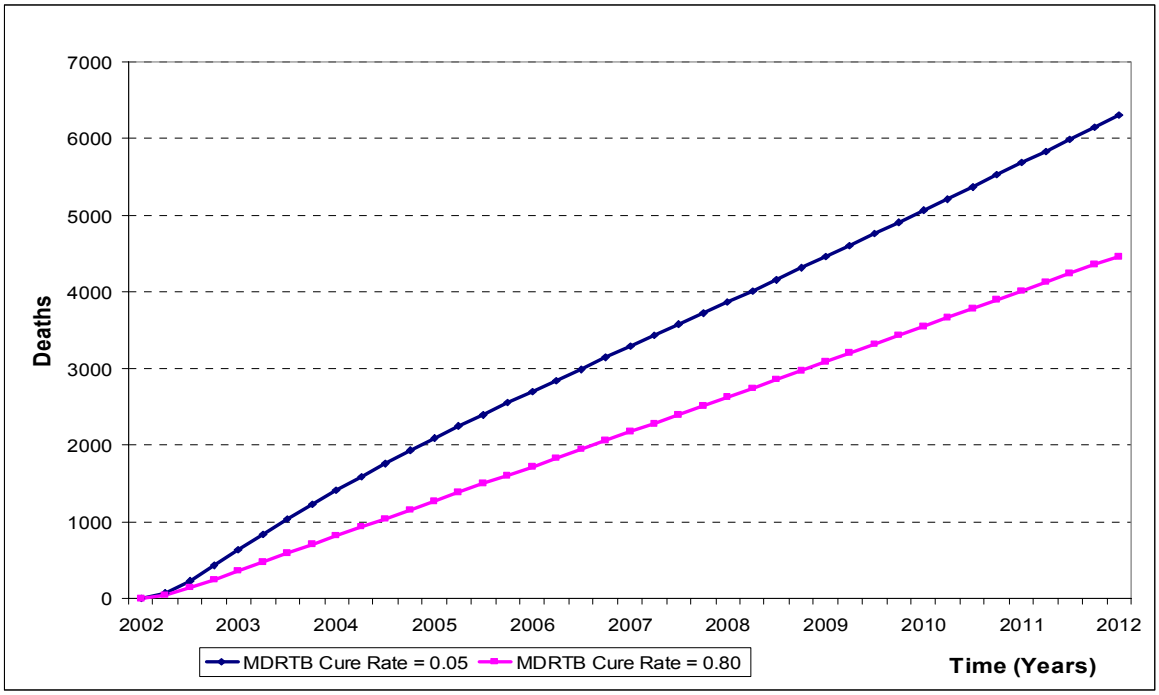

Figure 9: Cumulative deaths from tuberculosis

7.2 Cumulative deaths from MDRTB

This represents total deaths for individuals with MDRTB and includes deaths from HIV-associated MDRTB. This outcome is represented in Figure 10 for the two MDRTB cure rate scenarios. Under scenario 1, more than 1,900 deaths might be expected from MDRTB over the next ten years, approaching 30% of all deaths from tuberculosis. Moreover, the rate of increase in annual deaths under this scenario suggests a worsening epidemiological picture. Under scenario 2, only 134 deaths

would be expected. An effective MDRTB control programme may prevent 1,800 deaths over 10 years.

If the model is extended for 20 years, the cumulative death rates under the two scenarios differ considerably (figure 11). After 20 years approximately 4,500 excess cumulative deaths may occur if control for MDRTB remains poor.

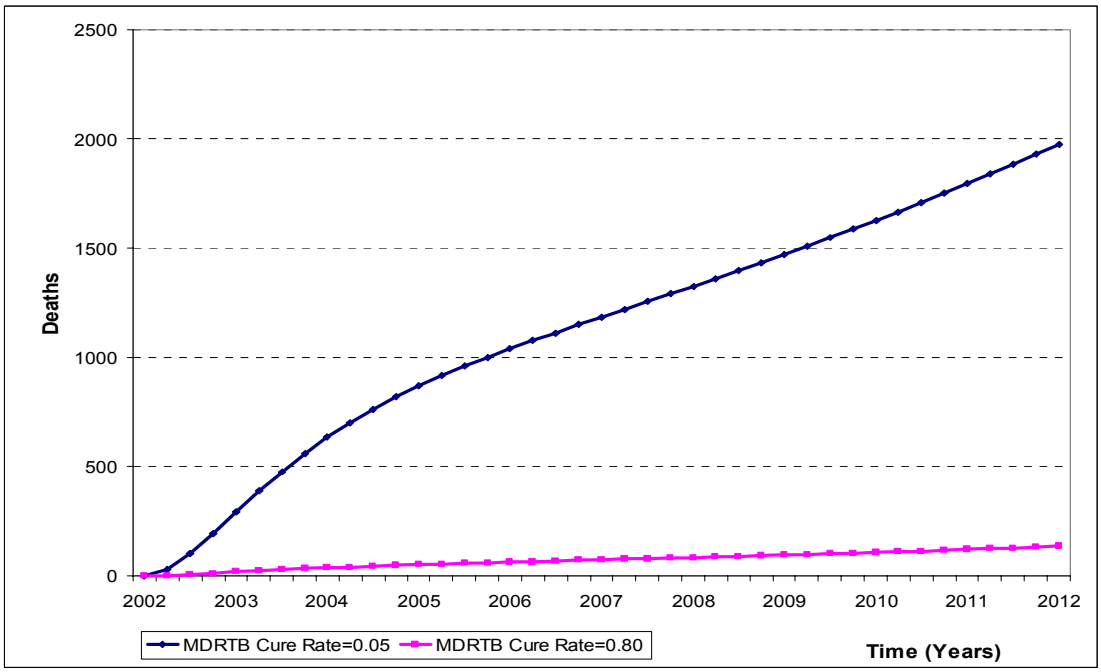

Figure 10: Cumulative deaths from MDRTB over a 10 years period

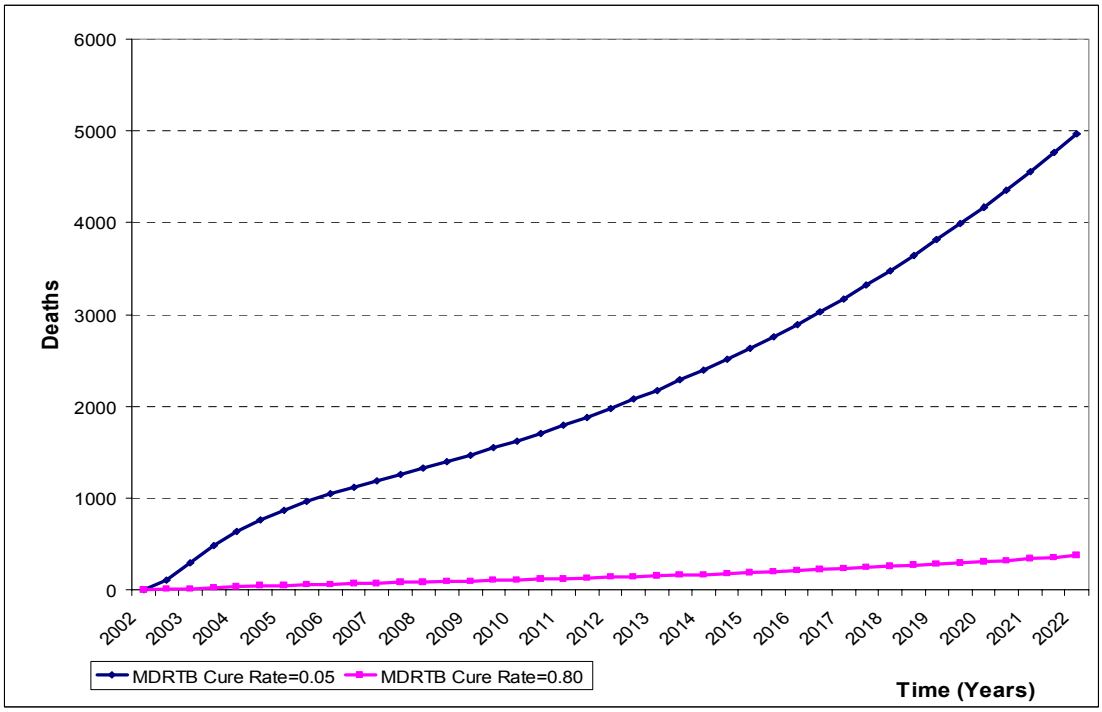

Figure 11: Cumulative deaths from MDRTB over a 20 years period

7.3 Cumulative deaths from HIV-associated tuberculosis

This includes deaths resulting from all forms of HIV-associated tuberculosis. This outcome over time is presented under the two scenarios in Figure 12. Under scenario 1, the model predicts 4,028 deaths cumulatively whilst under scenario 2, it predicts 3,800 deaths. That is, approximately 60% of cumulative deaths from tuberculosis under scenario 1, compared to 85% of deaths under scenario 2 are HIV-associated.

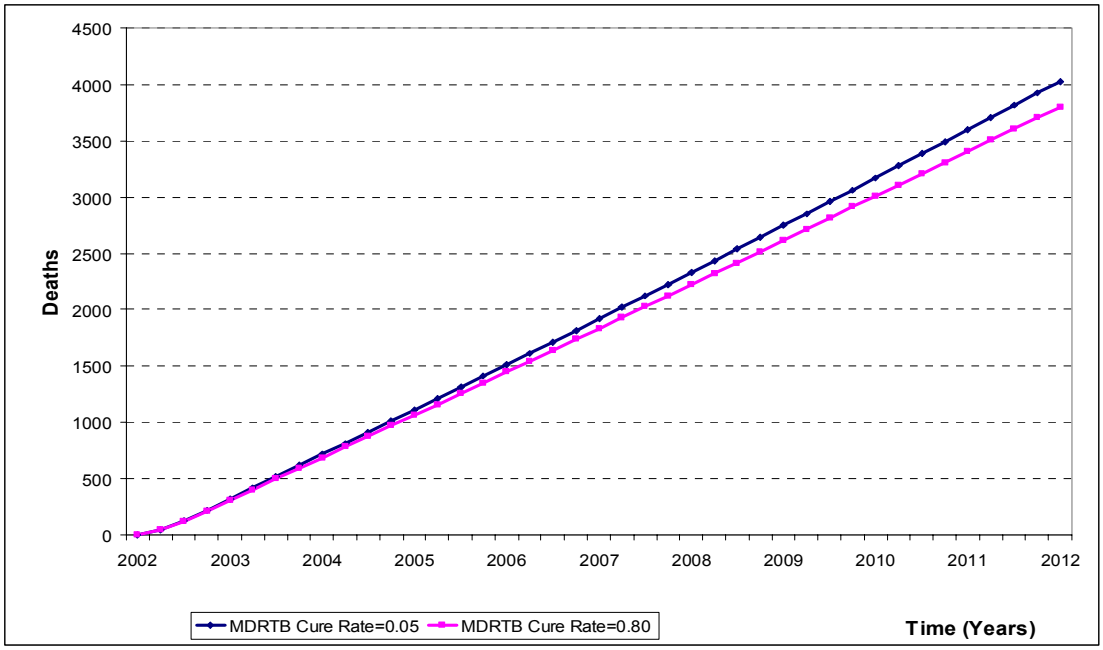

Figure 12: Cumulative HIV associated tuberculosis deaths

7.4 Cumulative deaths from HIV-associated MDRTB

This outcome is shown in figure 13 for both scenarios of MDRTB cure rate. The model predicts approaching 270 deaths cumulatively under scenario 1 in comparison to fewer than 50 for scenario 2. Although the number of cumulative deaths is relatively low under both scenarios, the rate of rise in annual deaths under scenario 1 is steep.

If the model is run for 20 years, the consequences of this are seen with more than nine times as many deaths occurring in those infected with HIV under scenario 1 compared to scenario 2 (figure 14).

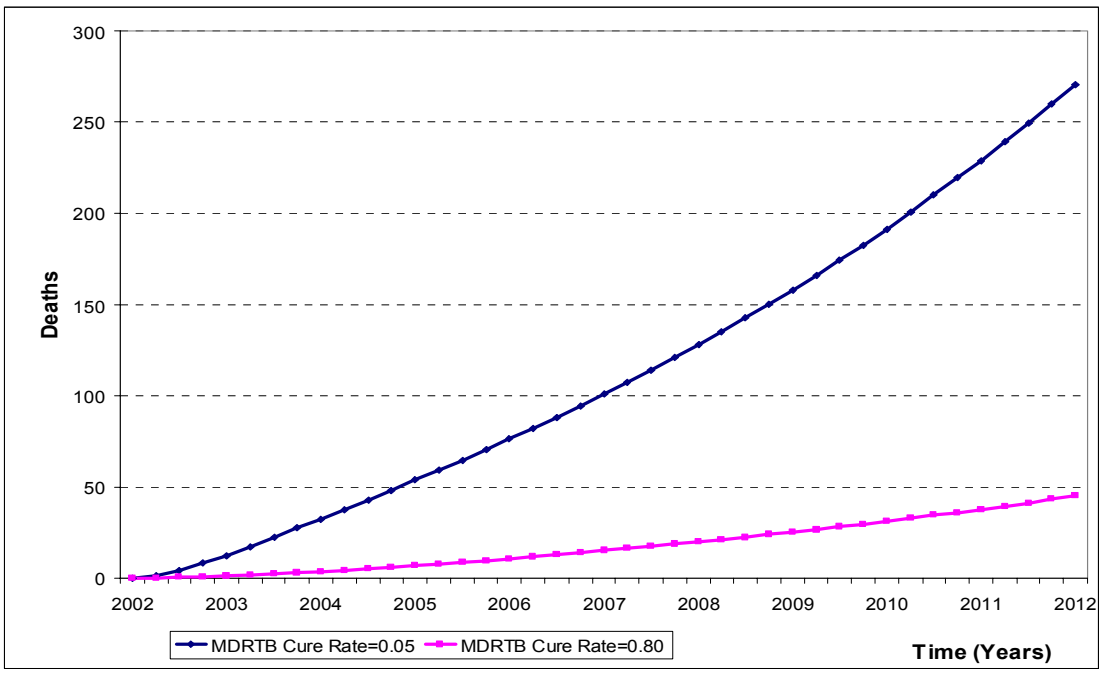

Figure 13: Cumulative deaths from HIV associated MDRTB over a 10 years period

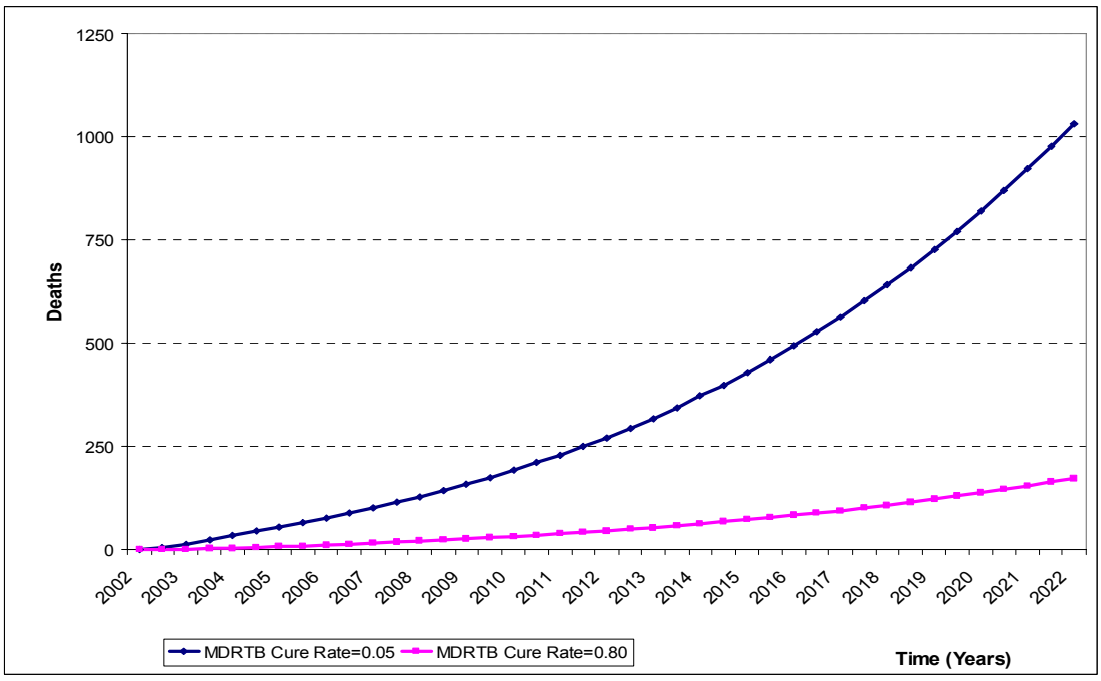

Figure 14: Cumulative deaths from HIV associated MDRTB over a 20 years period

8. Conclusions

The aim of the current research is to investigate the impact of MDRTB in settings of high HIV prevalence on the transmission dynamics of tuberculosis. Given that epidemics are complex systems involving interacting feedback loops, time delays, and non-linear relationships, we selected the System Dynamics (SD) methodology to represent and simulate tuberculosis transmission and spread and how they may be affected by different MDRTB control strategies.

The results indicate that if MDRTB treatment outcome is poor, a substantial number of deaths will occur. However, a significant number of these deaths can be avoided if effective MDRTB treatment policy such as the WHO DOTS-Plus strategy is adopted. Therefore, it is highly recommended that treatment using suitable combination of second line drugs is put n place if MDRTB spread is to be contained.

The model also indicates that HIV has an impact on MDRTB and tuberculosis deaths although the short and long term effects of HIV are different, an indicator of the dynamic complexity of epidemics transmission. In the short term, the number of deaths from HIV associated tuberculosis is not important as HIV is immature and the immune system of individuals is relatively intact. In the long term, however, the outcome is dramatically different. As more individuals get to the AIDS disease state, their immune system collapse leading to a rapid progress to the MDRTB disease state and, therefore, a rapid spread of this tuberculosis strain. If this process is coupled with poor MDRTB treatment, the net result is an explosion of deaths from HIV associated MDRTB, hence a high number of tuberculosis deaths.

Therefore, it is crucial that suitable actions are taken to improve MDRTB treatment (by extending, for example, the recommended WHO DOTS Plus program). Furthermore, it is crucial to address the underlying causes of HIV spread especially among the IDUs population to reduce the compounding effects of HIV on tuberculosis transmission dynamics and the resulting significant number of deaths.

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