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## Using a decision support systems computer simulation model to examine HIV and tuberculosis: the Russian Federation

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**Abstract:** The aim of this paper is to describe the development and use of a computer simulation model that can be used as a Decision Support System (DSS) to tackle the critical public health issues of HIV and HIV-related tuberculosis in the Russian Federation. This country has recently witnessed an explosion of HIV infections and a worrying spread of the Multi-Drug Resistant form of Tuberculosis (MDRTB). The conclusions drawn are that a high population coverage with Highly Active Anti-Retroviral Treatment (HAART) (75% or higher), allied with high MDRTB cure rates, reduces cumulative deaths by 60%, with limited impact below this level. This research offers a simulation model that can be applied as a DSS by public health officials to inform policy making. By doing so, ways of controlling the spread of HIV and MDRTB and reduce mortality from these serious public health threats is provided.

**Keywords:** electronic healthcare; HIV; tuberculosis; HAART; Russia; system dynamics; decision support systems.

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## 1 Introduction

In the Information Systems (IS) area when implementing IS, a solitary emphasis to technology cannot provide a successful system (Lyytinen and Hirschheim, 1987; Sauer, 1993). Instead, several aspects including the processes, interactions and impacts of the various stakeholders of the system need to be considered (Lyytinen and Hirschheim, 1987; Sauer, 1993). There are various types of organisations that are adopting IS, including, recently, healthcare providing establishments, such as hospitals, laboratories, primary care trusts and pharmacies. These establishments have also experienced failures during the implementation of IS and are searching for possible reasons, including the human aspects (Kushniruk and Borycki, 2008).

Researchers examining the healthcare context have found that IS implementation cannot be undertaken from a solely technological viewpoint, but issues related to human error, safety, risk and criticality need to be considered (Beynon-Davies and Lloyd-Williams, 1999; Hoyland and Aase, 2008). Similarly, Pouloudi (1998) established that when implementation does occur, a consideration of the stakeholders, i.e. a human and organisational perspective, is required. The health sector functions and operates as an organisation where decision making occurs with the support and visions from the management level; therefore, the role of management is pertinent (Glickman et al., 2007). Decision Support Systems (DSS) is the area of the Information Systems (IS) subject that is focused on supporting and improving managerial decision making (Arnott and Pervan, 2005). DSS are interactive computer-based systems intended to assist decision makers utilise data and models in order to identify and solve problems and make decisions. The “system must aid a decision maker in solving unprogrammed, unstructured (or ‘semistructured’) problems ... the system must possess an interactive query facility, with a query language that is easy to learn and use (Bonczek et al., 1981, p.19)”. DSS help managers/decision makers’ use and manipulate data; apply checklists and heuristics; and build and use mathematical models. In a DSS context, a model that can assist managers to form and implement informed decisions based on ‘what-if’ analysis, is based on reality and is not an abstraction or simplification of reality is a simulation model (Power, 2002). In more defined terms, Power (2002) describes a simulation model as ‘a technique for conducting experiments with a computer model’.

Currently the world’s health sector is gravely concerned and seeking ways of eliminating or reducing the numbers of deaths occurring from pandemics (Harper and Shahani, 2003). A pandemic that is causing the most anxiety is Human Immunodeficiency Virus (HIV). HIV is a retrovirus that can lead to Acquired Immuno Deficiency Syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections (Coffin et al., 1986; Sowadsky, 1999). As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS has killed more than 25 million people since it was first recognised on 1 December 1981, making it one of the most destructive pandemics in recorded history. It is estimated that about 0.6% of the world’s population is infected with HIV (Joint United Nations Programme on HIV/AIDS, 2006). According to the current estimates, HIV is set to infect 90 million people in Africa, resulting in a minimum estimate of 18 million orphans (Joint United Nations Programme on HIV/AIDS, 2005).

In countries with a high prevalence of HIV, tuberculosis (TB) incidence is also high and increasing (Girardi et al., 2000; WHO, 2003; Atun and Olynik, 2008). Growing evidence suggests that HIV has become a key driver of tuberculosis infection and subsequent mortality in many parts of the world (Currie et al., 2003; Williams and Dye, 2003; Vajpayee et al., 2004). Indeed, each year, 200,000 deaths from tuberculosis in sub-Saharan Africa are attributable to co-infection with HIV (Williams and Dye, 2003). Indeed as found in previous research, anti-retroviral treatment reduces both the mortality and the morbidity of HIV infection, but routine access to anti-retroviral medication is not available in all countries (Palella et al., 1998).

Where tuberculosis is multidrug-resistant (MDRTB), the challenges are even greater (Coker, 2004). Strategies designed to control tuberculosis, such as the WHO’s Directly Observed Therapy-Short course (DOTS), will have to be adapted if they are to meet the additional challenge of coincident HIV effectively and there have been calls for greater

integration of tuberculosis and HIV control programmes, with the addition of Highly Active Anti-Retroviral Treatment (HAART) to DOTS programmes. This important shift in public health policy demands critical analysis. Yet, to date, there has been little research to quantify the likely impact of provision of HAART in transitional societies, challenged simultaneously with high rates of MDRTB and explosive outbreaks of HIV.

In the last decade, the Russian Federation and Former Soviet Union (FSU) countries have witnessed an explosion of communicable diseases infections (Dubrovina et al., 2008; Schwalbe et al., 2008). Official data from the Russian Federation health authorities suggest that incidences of communicable disease infections increased almost three folds from 34 per 100,000 to 92 per 100,000 between 1991 and 2000 (Coker et al., 2004). Similarly, the death rate from tuberculosis increased from 8 per 100,000 in 1991 to 20 per 100,000 in 2001 (Floyd et al., 2006). Regarding HIV, the situation is even worse as the Russian Federation and FSU countries top the list of countries in terms of the disease growth as one million among 143 million Russians are believed to be infected with HIV (Coker et al., 2004). More worrying is the emerging evidence that tuberculosis and HIV are conspiring to amplify their spread in the population (Atun et al., 2007a; Atun et al., 2007b; Atun et al., 2008).

Although the social and economic conditions can be blamed partially for this situation, the health system structure in Russia bears a great degree of responsibility in this situation. The system is chronically under-funded, heavily dependent on outdated infrastructure and processes, and vertical, that is focusing on a single disease and ignoring its interactions with others (Coker et al., 2004). Legal, organisational and financial contexts have created a situation such that HIV control policies are ineffective (Atun et al., 2005a). Harm Reduction (HR) programmes designed to help those at risk of HIV infection cover a limited fraction of the population (Sarang et al., 2007; Tkatchenko-Schmidt et al., 2008). More disturbing is the fact that HR policies are not recognised within the Russian HIV control strategies and 70% of resources are provided by international donors (Rhodes et al., 2004).

As the scale of the communicable disease infections problem requires urgent and effective action in order to implement effectively and efficiently currently available clinical interventions, this research aimed *to describe the development and use of a computer simulation model that can be used as a Decision Support System (DSS) to inform the process of designing policies to tackle the critical public health issues of HIV and HIV-related Tuberculosis in the Russian Federation.*

By undertaking research such as this the benefits to the infectious diseases research area are immense. Having such a simulation model can allow the potential impact of several policy scenarios on deaths from tuberculosis to be considered; thereby informing the policy-making process. This means that policy makers will be able to determine using tangible evidence (simulation model) the impacts of their efforts (policies). For practitioners and industry, risks can be reduced since there will be a diagrammatic and visual model that is not an abstraction or simplification of reality, but can calculate the impacts (in terms of resources, labour, money and time). For academics, there will be more research (DSS and simulation) to consider in terms of HIV and HIV-related tuberculosis. Further benefits for industry lie in that there are many pharmaceutical companies seeking to determine the impacts of their medical treatments. By undertaking research such as this, the risk factor can be reduced and costs (monetary and time) can be reduced.

To acquaint the reader to this paper the structure of this paper is described. Following this section a background of Russia and the theoretical basis of DSS is provided. Following this, the research approach that was applied to obtain the findings is provided. Thereafter, the findings and analysis of this research is proffered. This is followed by a discussion of the research findings and finally, a conclusion of this paper is provided.

## **2 Background**

### *2.1 Russia, HIV and HIV-related tuberculosis*

Whilst concern over HIV sufferers in Africa grows, there are other parts of the world where the disease has made a huge impact and increased the numbers of sufferers. In Europe, Russia has the largest numbers of HIV sufferers' population. At the end of 2007, Russia had 1.6 million HIV sufferers and accounted for two-thirds of the HIV cases in Eastern Europe and Central Asia. There are 12 regions in Russia, including the major cities of Saint Petersburg and Moscow, where HIV prevalence rates are said to be 'above high', and a further 11 with high prevalence rates (UNAIDS, 2004a). The Deputy Prime Minister of Russia, Alexander Zhukov, has stated that 'the growth of AIDS has gone beyond a medical problem, and has become an issue of strategic, social and economic security of the country' (Klomegah, 2005).

European countries pledged to ensure universal access to treatment and care by 2005 across the whole of Europe and Central Asia and aimed to make sure 80% of 'high-risk' people had access to prevention services by 2010. However, at the end of 2004 only a small percentage of 'high-risk' people were being reached by prevention programmes (UNAIDS, 2004b). Cesar Chelala, an international public health consultant, noted that in April 2005 Russian prevention efforts were almost non-existent. On a positive note, in Central Asia a prevention project has been launched which will train medical workers and other people, and it is thought this and other treatment and prevention programmes could make a real difference in the area (Adams, 2005).

To assist drug users from drug-related harm, such as becoming infected with HIV, harm reduction programmes are being developed. Whilst these programmes do not deny the benefits of giving up the drugs altogether, they recognise that total abstinence is very difficult for addicts, and in some cases impossible. One aspect of a harm reduction programme is the introduction of needle exchanges where injecting drug users can exchange dirty needles for clean ones. If a clean supply of needles is available to injecting drug users then they will be less likely to share needles, therefore reducing the risk of contracting HIV. For example, in a major study of 81 cities around the world on HIV infection rates amongst injecting drug users IDUs, it was found that in 52 cities without needle exchanges HIV infection increased year on year, whilst in those cities with needle exchanges HIV infections decreased year on year (Dailey, 2002).

In addition to needle exchanges, harm reduction programmes also determine ways of encouraging IDUs to stop using drugs. One key way of doing this is by providing them with alternatives such as methadone. These alternatives are administered at clinics, and once inside, visitors can be offered further tests and treatment. Psychological assistance can be provided also, making the visitor feel valued and enriching their life.

Unfortunately, harm reduction services in Russia, Eastern Europe and Central Asia are not nearly adequate to meet demand. In general, authorities prefer to criminalise drug users rather than help them to give up drugs or avoid infection. In some countries – including Russia – substitution treatment with methadone is illegal (International Family Health, 2003).

Although Russian law guarantees people treatment, only around 16,000 (11%) of the 140,000 needing treatment were receiving it at the end of 2006. Coverage is much lower than in many poor African countries such as Zambia (35%), Malawi (43%) and Uganda (41%), which have much more severe epidemics (WHO, 2007). One reason for the low treatment figures is that medicines are very expensive. This is however becoming less of a problem, particularly in Russia. In early 2005, the Russian minister of health, Mikhail Zurabov, announced that agreements had been made with pharmaceutical companies which would reduce the amount an AIDS patient had to spend on medicines from US\$10,000 a year to around US\$3000 (Klomegah, 2005). The Russian government announced in late 2005 that it would make AIDS a priority and pledged to spend at least 20 times more on treatment and prevention in 2006 than it spent in 2005 (Bloomberg, 2005). A year later it was announced that spending would be doubled to US\$289 million in 2007 (Nowak, 2006). This increase has been aided by the Global Fund to Fight AIDS, TB and Malaria, which has pledged US\$209 million over five years for treatment programmes (Sargent, 2006). Yet although it is hoped that the extra money will enable a rapid expansion of treatment access in Russia, there are other issues to address besides funding, including pervasive discrimination and segregation. People living with HIV in Russia must attend special clinics for all of their medical needs. These clinics are isolated from the rest of the healthcare system and anyone who visits them risks being stigmatised. Moreover, the lack of integration means that doctors and nurses in non-specialist clinics have very little knowledge of HIV (Brown, 2006).

## *2.2 Theoretical basis*

DSS is a significant sub-field of IS scholarship with a research focus on development, technology, process and outcome studies (Arnott and Pervan, 2005). Much of the early work on DSS was highly experimental, even radical (Alter, 1980; Keen and Gambino, 1983). At the time, the aim of early DSS developers was to create an environment in which the human decision maker and the IT-based system worked together in an interactive fashion to solve problems; the human dealing with the complex unstructured parts of the problem, the information system providing assistance by automating the structured elements of the decision situation. The emphasis of this process was not to provide the user with a polished application programme that efficiently solved the target problem. In fact, the problems addressed are by definition impossible, or inappropriate, for an IT-based system to solve completely. Rather, the purpose of the development of a DSS was an attempt to improve the effectiveness of the decision maker.

The healthcare area has recognised the importance of DSS in decision making and is using it to conduct research in various contexts (Wickramasinghe and Goldberg, 2008; Yadav et al., 2009). Designed for, and in conjunction with, different HIV and AIDS clinics in Mumbai, India, a patient progress operational model of patient care has been developed to predict future patient numbers and associated healthcare costs. The suitably

detailed simulation model has been designed with flexibility, ease-of-use and lack of data in mind for developing country conditions. The model has been shown to yield a useful tool to aid decision making by clinicians and managers, thus helping in the provision of effective and efficient care to many HIV and AIDS patients throughout Mumbai and potentially the rest of India (Harper and Shahani, 2003).

In the UK, DSS is being used to develop a Clinical DSS (CDSS) for the paediatricians (Ramnarayan and Britto, 2002; Ramnarayan et al., 2007). Using the case study of a free, web-based CDSS titled ISABEL the researchers illustrate how using proprietary pattern recognition software called Autonomy ([www.autonomy.com](http://www.autonomy.com)) to search standard paediatric textbooks, a differential diagnostic tool produces a list of up to 15 diagnoses to consider for any given set of clinical features. Further decision support is provided by text, annotated images, and practice guidelines specific to each diagnosis.

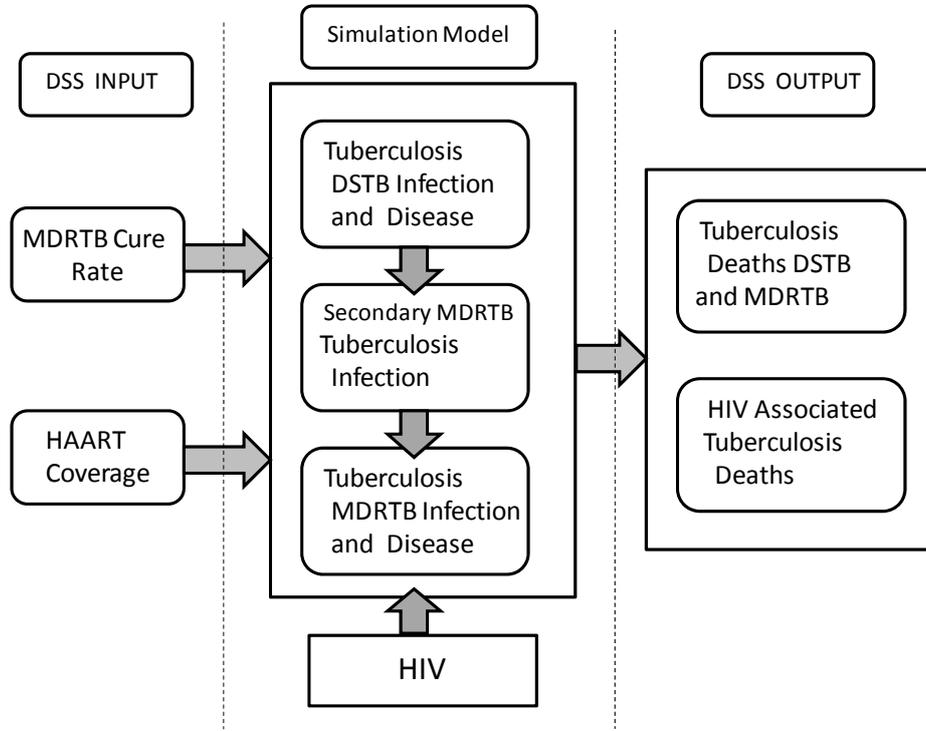
Breast cancer research has also attempted to utilise DSS. The study looked at the value of decision support in the initial assessment ('Triple Assessment') of women referred to specialist breast clinics. A collaborating breast surgeon used PROforma to formalise national guidelines for genetic risk assessment and for decisions about imaging (mammography and ultrasound), biopsy and management (Fox et al., 2006).

Therefore, it can be learnt that DSS is being considered useful for decision making in the healthcare sector and not only for design, development and implementation issues in IS research.

### **3 Research approach and the decision support system**

A System Dynamics (SD) simulation model (Sterman, 2000) was developed to represent the transmission dynamics of tuberculosis and HIV. SD methodology was chosen because the transmission of infectious diseases is complex, involving many interacting variables, interconnected feedback loops and non-linear cause-effect relationships. Given the dynamic complexity of these systems, their behaviour is generally difficult to predict. Formal system-based modelling approaches, such as SD, can represent these systems, simulate their behaviour and predict the impact of health system interventions to support policy makers in determining the most appropriate actions to improve health outcomes (Dangerfield et al., 2001; Cohen et al., 2009)

The SD model was used to assess the impact of implementing internationally recommended policies on the spread of these two diseases including the resulting deaths over the next decade in a region of the Russian Federation. The simulation model was designed to be friendly and easy to use to allow public health decision makers and medical staff, with limited knowledge in computing, to easily use it in order to simulate scenarios and get their results. As such the simulation model acted as a DSS to help decision makers in different parts of the public health system conduct experiments, analyse results, learn about the complexity of the two diseases and come to a shared understanding of the rationale to implement the policies derived from the simulation model (See Figure 1 for a high-level structure of the DSS).

**Figure 1** General structure of the decision support system simulation model

### 3.1 Model development

The first phase in the model development aimed to understand the epidemiology of TB and HIV including the processes of infection and transmission of these diseases in the population. This phase was important as it allowed the research team, local clinicians and policy makers from the Ministry of Health in Samara to jointly develop a better understanding of the factors that influence the spread of TB as well as the mechanisms of its transmission in the population. This phase also enabled the local counterparts to understand the complexity of the TB control system that they would be operating, and to appreciate the importance of holistic and systemic approaches associated with understanding and applying such a system.

The research team obtained ethical approval from the local research ethics committee, and permission from the regional Ministry of Health to access epidemiological, health services and financing data. A multidisciplinary design team, comprising local and international researchers involved in the project, was established to include clinicians, health system and public health specialists and microbiologists with knowledge and experience of modelling TB and HIV. The members of the design team worked closely with policy makers; thereby being aware of the local, national and international issues relevant to policy makers. Through an iterative process of discussions and triangulation, drawing on the expertise of the group and published literature, model components and details were developed, parameters identified and the model populated. Local

practitioners, experts and policy makers were also involved in discussions in model development, test assumptions, check model validity and in scenario planning. This led to the construction of the transmission dynamics model for TB and HIV which is described below.

In order to verify that the relevant and correct data and information was being obtained, several visits were made by the research team to Samara. There was an occurrence of interviews with key informants and visits to provider units where TB services were delivered. The structure of TB and HIV transmission dynamics were determined drawing on the published literature and the knowledge base of team members, complemented by interviews with clinicians and public health specialists in Samara. The literature review and discussions among the research team members led to an initial, high-level, simplified map of the disease epidemiology. Following this, around 20 interviews were conducted in Samara with a broad set of stakeholders, comprising clinicians, nurses, managers from healthcare provider facilities, and policy makers from the Ministry of Health. The map was presented to interviewees and iteratively refined following comments. The map was ‘frozen’ once all interviewees agreed on its structure.

The second phase of the development focused on the building of the computer simulation model. This phase was divided into two stages. First, we constructed a tuberculosis transmission dynamics model – including disease, detection and treatment of both DSTB and MDRTB. Second, we extended the model by adding HIV/AIDS, including acquisition and spread of HIV, development of AIDS and the effects of treatment with HAART for individuals with late-stage HIV or AIDS.

### *3.1.1 Model of DSTB transmission*

The natural history of tuberculosis transmission is represented by a stock and flow structure in which individuals move from the state of ‘susceptible individuals’ to the state of ‘latently infected individuals’. From the latently infected state, some individuals progress to the ‘DSTB disease’ state rapidly, whereas others progress slowly (Blower et al., 1996). Without therapeutic interventions, individuals with disease may die, develop persistent disease or ‘self-cure’ (Vynnycky and Fine, 1999).

The model incorporates a therapeutic intervention for individuals who have progressed to the ‘DSTB disease’ state. These individuals, when detected, enter a drug treatment phase for the first time. They may die, be cured or develop persistent disease. Those with persistent disease may remain in that state, die or return to treatment at a later stage, a state from which, again, they may remain, die or be cured.

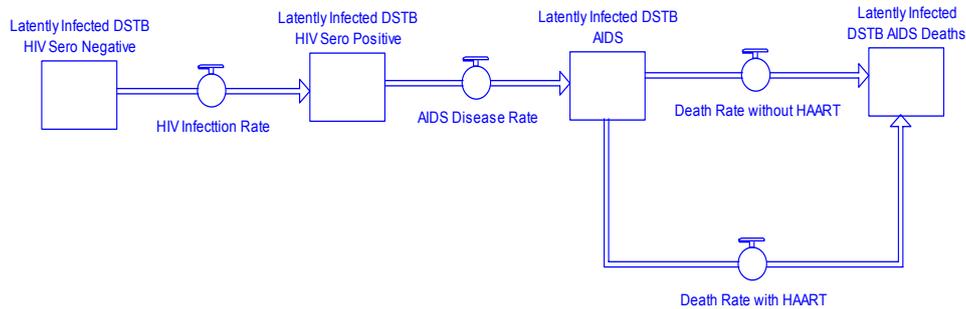
### *3.1.2 Model of MDRTB transmission*

From the interview findings it was revealed that two processes drive the spread of MDRTB. First, individuals with DSTB entering treatment for the first time may develop MDRTB – a process known as secondary or acquired infection. Second, susceptible individuals who come in contact with individuals with acquired MDRTB may develop tuberculosis with a multidrug-resistant strain of *Mycobacterium tuberculosis*, a process known as primary MDRTB (Tahaoglou et al., 2001). These individuals progress to the ‘MDRTB disease’ state rapidly or slowly, in a similar fashion to DSTB. Individuals with MDRTB enter a treatment phase from which they may progress to three states: death, cure or persistent MDRTB.

### 3.1.3 Model of HIV transmission

The HIV transmission sub-system model assumes individuals will be in one of three states: (i) HIV seronegative, (ii) HIV seropositive or (iii) AIDS. Any individual represented in any of the states described in the tuberculosis model will also be represented in one of the three states described in the HIV transmission model. Figure 2 presents the HIV transmission process for one specific tuberculosis state, ‘latently infected DSTB’.

**Figure 2** The HIV/AIDS transmission sub-system for the tuberculosis state ‘Latently Infected DSTB’ (see online version for colours)



Given that in the Russian Federation a very high proportion of HIV-seropositive individuals acquired HIV through intravenous drug use and a small proportion through secondary sexual spread, the model restricts transmission to the intravenous drug use route (Rhodes et al., 2002). The transmission risk of moving from HIV-seronegative to HIV-seropositive state depends on: (i) the average number of injections per unit time, (ii) the probability that the injection equipment is contaminated with HIV, (iii) the probability of HIV transmission and (iv) the prevalence of Intravenous Drug Users (IDUs) in the overall adult population (Grassly et al., 2002). For the purposes of our model, the proportion of the population who are IDUs is assumed to remain constant.

Individuals who become HIV seropositive are assumed to progress over a period of 10 years to develop AIDS. Due to the breakdown in the immune system that results, co-infection with DSTB or MDRTB means that these individuals will progress faster to the corresponding disease states than individuals without AIDS. If an individual with AIDS is not treated with HAART, it is assumed that they will die within two years. However, individuals treated with HAART may live for a period of 10 years after reaching the AIDS disease state. Furthermore, if an individual co-infected with AIDS and tuberculosis is treated with HAART, their disease progression is similar to that of an individual without HIV/AIDS.

## 4 Parameter estimation and model validation

The parameters in the model have been drawn from published estimates in archival medical reports and, where these are unavailable, explicit assumptions deemed to be close to real life situations (confirmed by the interviews and discussions) were made. We identified studies through a systematic Medline search and obtained data from

locally collected routine statistics. Tables showing tuberculosis transmission parameters corresponding to the HIV-seronegative, HIV-seropositive and AIDS states are not shown but are available from the authors on request.

To validate the model before its use for scenario analysis, trends were compared against available data regarding cumulative tuberculosis deaths in Samara Oblast from 1997 to 2002. The model replicated, with a high level of accuracy, the real-world dynamics of the most important variables such as tuberculosis prevalence and cumulative deaths (Atun et al., 2005b)

## **5 Interventions and scenarios**

Following the interviews with the practitioners and other related personnel the scenarios were created. The scenarios tested in the model included policies related to the effectiveness of MDRTB treatment and the level of population coverage with HAART treatment. With respect to MDRTB, two effectiveness levels are selected: (i) 5% cure rate and (ii) 80% cure rate. The first level reflects documented outcomes of DOTS programmes implemented in Russia (Centers for Disease Control and Prevention, 1999). The second level represents what can be potentially achieved with a well-resourced and well-organised MDRTB control programme with access to second-line drugs (Mitnick et al., 2003). With respect to HAART coverage, five possible scenarios ranging from no population coverage (0%) to full coverage of all individuals infected with HIV who are likely to benefit (100%) with 25% increments, including 25%, 50% and 75% coverage. The impact of these scenarios on the cumulative deaths from tuberculosis, MDRTB and deaths associated with AIDS were analysed. Under all the scenarios, it was assumed that there was a case detection rate of 70% for cases of infectious tuberculosis and 85% treatment success rate for cases of Drug Susceptible Tuberculosis (DSTB), in line with targets set by the WHO.

### *5.1 Scenario analysis parameters*

Scenario analysis parameters include MDRTB cure rate and HAART population coverage. MDRTB cure rate is assigned to two levels: 5% and 80%. HAART population coverage varies from 0% (no coverage) to 100% (full coverage) with increments of 25%. The time frame for the simulation model is 10 years and is assumed to start at the beginning of 2003 and finish at the end of 2012. The initial values in the simulation correspond to the number of adults in each of the tuberculosis and HIV states represented in the model at the beginning of year 2003. These values are presented in Table 1.

### *5.2 Model outputs*

The model predicts the following outcomes: (i) cumulative deaths from tuberculosis that includes deaths from all forms of tuberculosis and deaths from HIV-associated tuberculosis; (ii) cumulative deaths from HIV-associated tuberculosis and (iii) cumulative deaths from HIV-associated MDRTB.

**Table 1** Initial conditions for the simulation model reflecting estimated situation in Samara Oblast (January 2003)

<i>Stock (Variable State)</i>	<i>Initial value in the Simulation Model</i>
Susceptible TB – HIV (seronegative)	1,608,596
Susceptible TB – HIV (seropositive)	12,044
Latently Infected DSTB – HIV (seronegative)	681,408
Latently Infected DSTB – HIV (seropositive)	4862
Disease DSTB – HIV (seronegative)	1400
Disease DSTB – HIV (seropositive)	100
Disease MDRTB – HIV (seronegative)	1146
Disease MDRTB – HIV (seropositive)	44

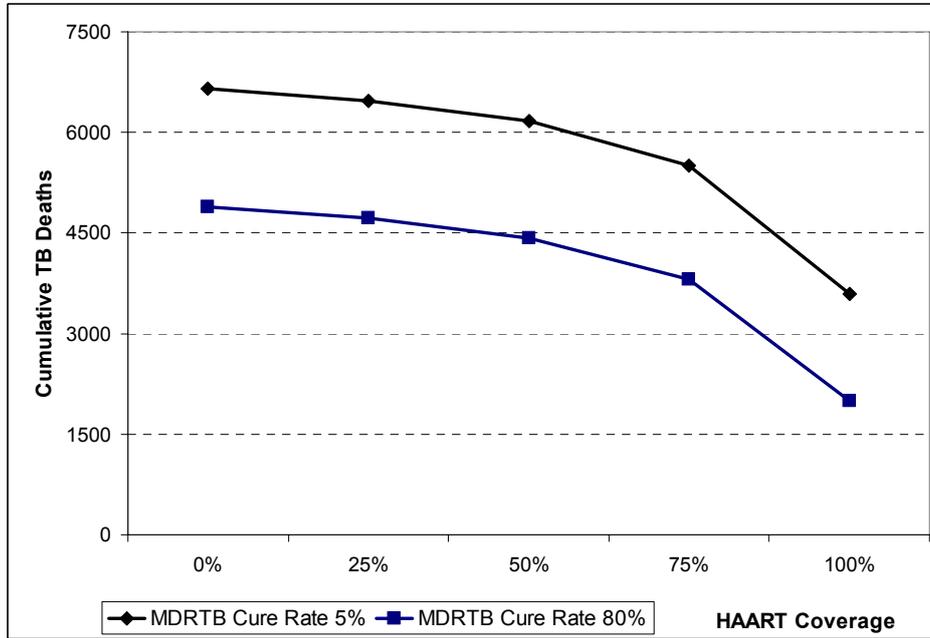
## 6 Findings

Samara Region has a total population of 3.3 million people, of whom 1.6 million are adults. In January 2003, the estimated prevalent number of individuals with tuberculosis was 2690, of whom 40% had MDRTB (Table 1). The region has experienced an explosive epidemic of HIV, and by January 2003 there were an estimated 17,000 prevalent cases (Table 1).

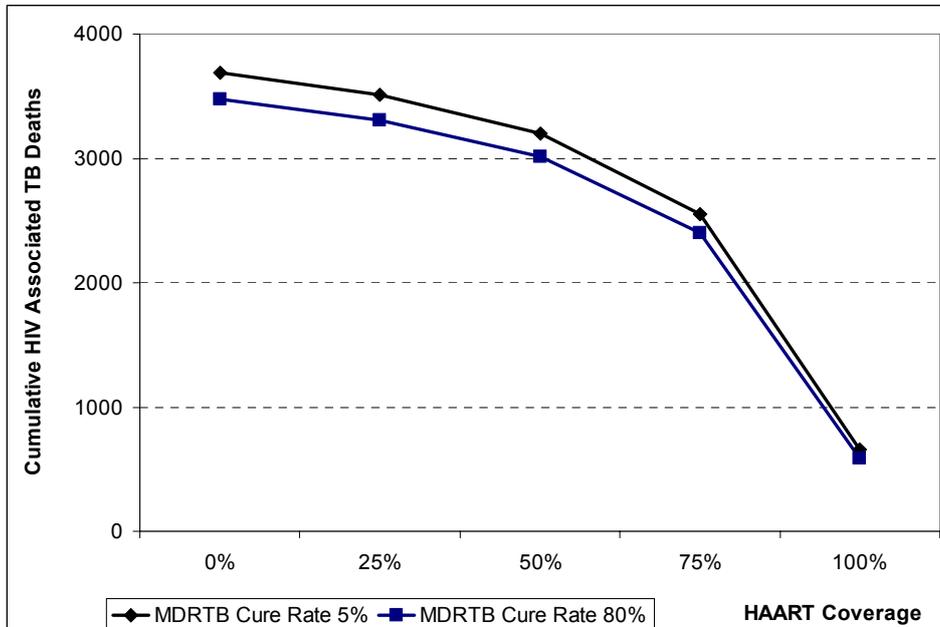
The cumulative deaths from tuberculosis, with two levels of MDRTB cure rate of 5% and 80% and the five levels of HAART coverage (from 0% to 100%), are presented in Figure 3. The results indicate that in the 10-year period of simulation, in the absence of HAART coverage, the cumulative number of tuberculosis deaths will be 6650 with an MDRTB cure rate of 5%, but will decline to 4888 if MDRTB cure rates reach 80%. With an increase in HAART coverage, the cumulative number of tuberculosis deaths initially declines at a slow rate as long as coverage rates are below 50%. Between 50% and 75% the rate of decline increases, but with coverage rates of 75% and beyond, the rate of decline increases significantly. Hence, the cumulative number of deaths from tuberculosis at 5% and 80% MDRTB cure rates decline: (i) with 25% HAART coverage by 3% to 6473 at 5% MDRTB cure rate and 3% to 4721 at 80% MDRTB cure rate, respectively; (ii) with 50% HAART coverage by 7% to 6162 and 9% to 4428; (iii) with 75% HAART coverage by 17% to 5505 and 22% to 3808 and (iv) at 100% HAART coverage declines substantially by 46% to 3595 and 60% to 1993, respectively (Figure 3).

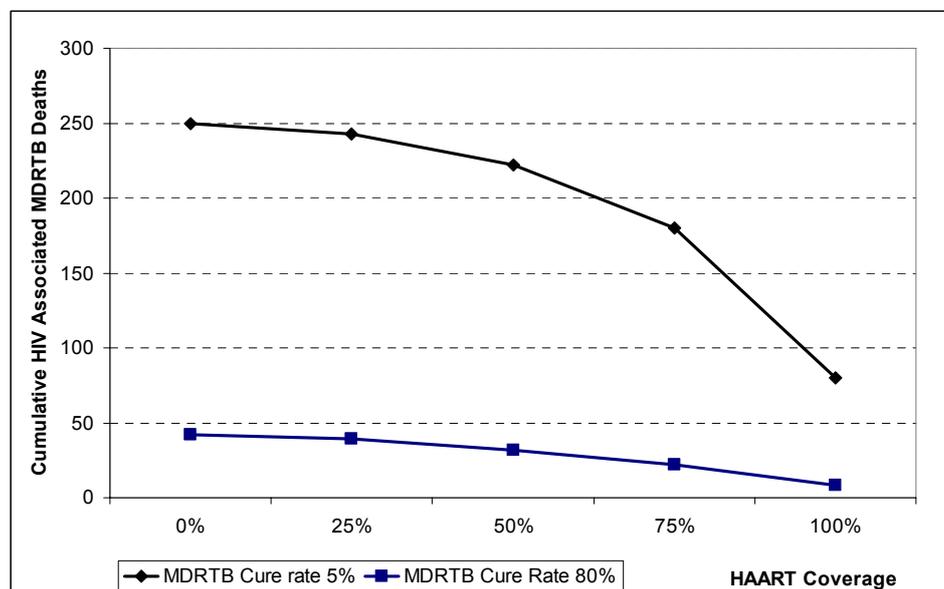
Cumulative deaths from HIV-associated tuberculosis with no HAART coverage reach 3686 and 3473 when MDRTB cure rates are, respectively, 5% and 80% (Figure 4). At 5% and 80% MDRTB cure rates, cumulative HIV-associated MDRTB deaths decline in a non-linear manner: (i) at 50% diminish by 68% to 80 and by 80% to eight with 5% and 80% MDRTB cure rates, respectively (Figure 5).

**Figure 3** Cumulative deaths at 10 years from tuberculosis at varying HAART coverage levels and MDRTB cure rates of 5% and 80% (see online version for colours)



**Figure 4** Cumulative HIV-associated tuberculosis deaths at 10 years at varying HAART coverage levels and with MDRTB cure rates of 5% and 80% (see online version for colours)



**Figure 5** Cumulative HIV-associated MDRTB deaths at 10 years (see online version for colours)

## 7 Discussion

For this research a setting where there is currently a high prevalence rate of MDRTB and an immature, contained epidemic of HIV in IDUs, the epidemic of MDRTB was used. If left unchallenged with effective MDRTB treatment but in particular high HAART coverage, this may result in a substantial number of deaths from tuberculosis.

Many deaths from tuberculosis, HIV-associated tuberculosis and HIV-associated MDRTB can be averted with effective tuberculosis and MDRTB control strategies that achieve high MDRTB cure rate and coverage of HIV-infected people with HAART. However, the rate of decline in the cumulative number of deaths is not linearly proportional to the rate of increase in HAART coverage. Instead, we observed a slow change in the rate of decline for cumulative deaths from tuberculosis, HIV-associated tuberculosis and HIV-associated MDRTB up to 50% HAART coverage rates. The rate of decline increases between 50% and 75% HAART coverage and more substantially between 75% and 100% coverage. This relationship holds good for both 5% and 80% MDRTB cure rates.

For research, these findings have important policy implications. At low HAART coverage rates, the impact on cumulative deaths is minimal, but the impact increases substantially at coverage rates above 50% and particularly above 75%.

Current policy recommendations for HAART coverage focus on scaling up but do not explicitly identify an optimal coverage target (World Health Organization, 2005). It is demonstrated that in the epidemiological setting described above, scaling up HAART coverage to levels up to 50% is likely to achieve minimal impact, with an appreciable impact on mortality only becoming apparent at 50–75% coverage and becoming substantial only at 75% coverage level and beyond.

HAART coverage by 13% to 3204 and 14% to 3014; (i) at 75% coverage by 31% to 2552 and 32% to 2396 and (ii) beyond 75% coverage, the number of deaths declines substantially so that when 100% HAART coverage is achieved, HIV-associated tuberculosis deaths fall by 83% to 657 and by 84% to 585, respectively (Figure 4). The acceleration in the decline in death rates beyond 75% is much faster for HIV-associated tuberculosis deaths than for tuberculosis only deaths.

In the absence of any HAART coverage, the cumulative number of deaths from HIV-associated MDRTB is 250 at 5% and 42 at 80% MDRTB cure rates, respectively. The cumulative number of HIV-associated MDRTB deaths declines substantially with HAART coverage of 75% and beyond, and at 100% HAART the number of deaths reaches 80 at 5% and 8 at 80% MDRTB cure rates.

The non-linear relationship between increased HAART coverage and decline in cumulative death rates can be explained by the complex interactions at play between different elements of the tuberculosis and HIV transmission systems. Systems with complex relationships, which include feedback loops, behave in a non-linear manner and may respond in counter-intuitive ways to interventions, which are designed to influence system elements (Sterman, 1989). This may result in 'policy resistance'. One way to reduce this policy resistance is to adopt 'systems thinking', which requires a detailed analysis of these system elements and the ways they interact (Senge, 1990)

## 8 Conclusions

In terms of the aim stated at the outset of this paper it can be learnt that development and implementation of a simulation model such as the one suggested in this paper is a complex and iterative issue, but highly regarded as essential. HIV and HIV-related pandemics are occurring around the globe in incremental numbers and is a grave concern that needs to be examined and rescued or eliminated. However, although this research has important implications, it is still in development stages and limited in a number of ways.

First, the model assumes a static age structure such that younger cohorts of individuals, who may be at risk of tuberculosis and HIV, are not considered within the model. It is assumed that as cohorts age, they are likely to influence the transmission dynamics of these two infections. The extent of the HIV epidemic may be underestimated in the model because the population at risk of HIV, which is the IDU population, remains static. In reality, it is likely that new young people will enter this population, swelling its ranks. Research is continuing to include age structure and wider transmission of HIV in this model. Similarly, the model does not include the consequences of population migration to and from the region. The Samara region, however, has a relatively stable population and was chosen as the population to model, in part, for this reason. Any changes in this pattern of population movement could impact upon predictions. It is assumed that the HIV spread will be contained within the IDU population, which is a further limitation. In future it is likely that there will be significant sexual spread that will lead to leakage outside this population. These factors are expected to lead to an underestimation of the likely epidemic of HIV in the region and, consequently, of the impact with tuberculosis dynamics.

In practice, both HIV and tuberculosis tend to cluster in certain sub-populations, and micro-epidemics may occur, for example, through institutional spread within prison settings or in tuberculosis hospitals. Our model does not predict such scenarios and, consequently, may again underestimate the likely impact of such enhanced transmission dynamics. The model does not take into account possible policy changes. In our model, for example, the number of contacts per unit time between tuberculosis-susceptible and tuberculosis-infected individuals is assumed to be constant, and the model does not account for quarantine or isolation policies or changes in, for example, contact rates due to reactions from susceptible individuals to perceived risks in infected groups. The same assumptions hold good regarding the rate of acquiring HIV. The rate of movement from the HIV-seronegative state to the HIV-seropositive state is assumed to be constant regardless of the individual's tuberculosis state, a factor that might be influenced, for example, by institutional care practices and the patient's behaviour within institutions. Notwithstanding these limitations, we believe that the findings are sufficiently robust to inform policy.

However, despite these limitations this research has important implications and if developed further in the future offers pertinent results and implications. We foresee the future as being one where the research will be focused upon considering some of the variables that we could not consider due to the setting or the sample population that utilised. Further, to ensure that the practitioners and other individuals requiring the application will be able to do and offer advice and support when required the foreseen strategy is being viewed as one where implementation will occur by utilising the simulation model as a web-based model. This way accessibility will be offered 24/7 and from any location anywhere around the globe. This way, practitioners can access the model when required and offer advice to patients when advice and support are required.

For governments, and funding agencies such as the WHO, the World Bank and the Global Fund our research has important implications as they are investing significant funds to control the tuberculosis, MDRTB and HIV epidemics in post-Soviet countries. The investment in HAART should be large enough to scale up coverage to 75% of the HIV-seropositive population to have a significant impact on tuberculosis and HIV-associated deaths. Incremental scale-up at low levels of coverage will have limited success in averting deaths. For HIV-associated tuberculosis deaths, provision of HAART alone is likely to be more effective public health strategy than provision of effective MDRTB treatment alone.

## References

- Adams, L. (2005) 'Needle-sharing, unprotected sex fuel HIV-AIDS in Former Soviet Union', *VOA News*, August.
- Alter, S.L. (1980) *Decision Support Systems: Current Practice and Continuing Challenges*, Addison-Wesley, Reading.
- Arnott, D. and Pervan, G. (2005) 'A critical analysis of decision support systems research', *Journal of Information Technology*, Vol. 20, pp.67–87.
- Atun, R. and Olynik, I. (2008) 'Resistance to implementing policy change: the case of Ukraine', *Bulletin of the World Health Organization*, Vol. 86, pp.147–154.
- Atun, R., McKee, M., Drobniewski, F. and Coker, R. (2005a) 'Analysis of how the health systems contexts shapes responses to the control of human immunodeficiency virus: case studies from the Russian Federation', *Bulletin of the World Health Organization*, Vol. 83, pp.730–738.

- Atun, R.A., Lebcir, R., Drobniewski, F. and Coker, R.J. (2005b) 'Impact of an effective multidrug resistant tuberculosis control programme in the setting of an immature HIV epidemic: system dynamics simulation model', *International Journal of STD and AIDS*, Vol. 16, pp.560–570.
- Atun, R.A., Lebcir, M.R., Drobniewski, F., McKee, M. and Coker, R.J. (2007a) 'High coverage with HAART is required to reduce substantially the number of deaths from tuberculosis: system dynamics simulation', *International Journal of STD and AIDS*, Vol. 18, pp.267–273.
- Atun, R.A., Lebcir, M.R., McKee, M., Habicht, J. and Coker, R.J. (2007b) 'Impact of joined-up HIV harm reduction and multidrug resistant tuberculosis control programmes in Estonia: system dynamics simulation model', *Health Policy*, Vol. 81, pp.207–217.
- Atun, R.A., McKee, M., Coker, R. and Gurol-Urganci, I. (2008) 'Health systems' responses to 25 years of HIV in Europe: inequities persist and challenges remain', *Health Policy*, Vol. 86, pp.181–194.
- Beynon-Davies, P. and Lloyd-Williams, M. (1999) 'Health information systems, safety and organisational learning', *Health Informatics*, Vol. 4, pp.128–137.
- Bloomberg.com (2005) *Putin says AIDS problem 'Serious', spending to increase 20-fold*. Available online at: <http://www.bloomberg.com> (accessed on September 2005).
- Blower, S.M., Small, P.M. and Hopewell, P. (1996) 'Control strategies for tuberculosis epidemics: new models for old problems', *Science*, Vol. 273, pp.497–500.
- Bonczek, R.H., Holsapple, C.W. and Whinston, A.B. (1981) *Foundations of Decision Support Systems*, Academic Press.
- Brown, H. (2006) 'Russia's blossoming civil society holds the key to HIV', *The Lancet*, Vol. 368, p.9534.
- Centers for Disease Control and Prevention (1999) 'Primary multidrug-resistant tuberculosis – Ivanovo Oblast, Russia', *MMWR*, Vol. 8, pp.661–664.
- Coffin, J., Haase, A., Levy, J.A., Montagnier, L., Oroszlan, S., Teich, N., Temin, H., Toyoshima, K., Varmus, H., Vogt, P. and Weiss, R.A. (1986) 'What to call the AIDS virus?', *Nature*, Vol. 321, p.6065.
- Cohen, T., Dye, C., Colijn, C., Williams, B. and Murray, M (2009) 'Mathematical models of the epidemiology and control of drug-resistant TB', *Expert Review of Respiratory Medicine*, Vol. 3, pp.67–79.
- Coker, R.J. (2004) 'Multidrug resistant tuberculosis: public health challenges', *Tropical Medicine and International Health*, Vol. 9, pp.25–40.
- Coker, R., Atun, R. and McKee, M. (2004) 'Health care system frailties and public health control of communicable disease on the European Union's new eastern border', *Lancet*, Vol. 363, pp.1389–1392.
- Currie, C.S.M., Williams, B.G., Cheng, R.C.H. and Dye, C. (2003) 'Tuberculosis epidemics driven by HIV: is prevention better than cure?', *AIDS*, Vol. 17, pp.2501–2508.
- Dailey, E. (2002) 'The rights approach is the right approach to harm reduction in Central Asia', *Newsletter of the International Harm Reduction Programme of the Open Society Institute*, Vol. 3, p.20.
- Dangerfield, B.C., Fang, Y. and Roberts, C.A. (2001) 'Model-based scenarios for the epidemiology of HIV/AIDS: the consequences of highly active antiretroviral therapy', *System Dynamics Review*, Vol. 17, pp.119–150.
- Dubrovina, I., Miskinins, K., Lyepshina, S., Yann, Y., Hoffman, H., Zaleskis, R., Nunn, P. and Zihnoj, M. (2008) 'Drug resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics?', *The International Journal of Tuberculosis and Lung Disease*, Vol. 12, pp.756–762.
- Floyd, K., Hutubessy, R., Samyshkin, Y., Korobitsyn, A., Fedorin, I. and Volchenkov, G. (2006) 'Health systems efficiency in the Russian Federation: tuberculosis control', *Bulletin of the World Health Organization*, Vol. 84, pp.43–51.
- Fox, J., Patkar, V. and Thomson, R. (2006) 'Decision support for health care: the PROforma evidence base', *Informatics in Primary Care*, Vol. 14, pp.49–54.

- Girardi, E., Raviglione, M.C., Antonucci, G., Godfrey-Faussett, P. and Ippolito, G. (2000) 'Impact of the HIV epidemic on the spread of other diseases: the case of tuberculosis', *AIDS*, Vol. 14 (Supp 3).
- Glickman, S.W., Baggett, K.A., Krubery, C.G., Peterson, E.D. and Schulman, K.A. (2007) 'Promoting quality: the health-care organization from a management perspective', *International Journal for Quality in Health Care*, Vol. 19, pp.341–348.
- Grassly, N., Lowndes, C., Rhodes, T., Judd, A., Renton, A. and Garnett, G.P. (2002) 'Modelling emerging HIV epidemics: the role of injection drug use and sexual transmission in the Russian Federation, China and India', *International Journal of Drug Policy*, Vol. 14, pp.25–43.
- Harper, P.R. and Shahani, A.K. (2003) 'A decision support system for the care of HIV and AIDS patients in India', *European Journal of Operational Research*, Vol. 147, pp.187–197.
- Hoyland, S. and Aase, K. (2008) 'An exploratory study on human, technological and organisational interactions within healthcare', *Safety Science Monitor*, Vol. 12, p.1.
- International Family Health (2003) *HIV/AIDS and drug misuse in Russia: harm reduction programmes and the Russian legal system*.
- Joint United Nations Programme on HIV/AIDS (2005) 'Overview of the global AIDS epidemic', *Report on the global AIDS epidemic* (PDF format).
- Joint United Nations Programme on HIV/AIDS (2006) 'Overview of the global AIDS epidemic', *Report on the global AIDS epidemic* (PDF format).
- Keen, P.G.W. and Gambino, A.J. (1983) 'Building a decision support system: the mythical man-month revisited', in Bennett, J.L. (Ed.): *Readings in Decision Support Systems*, Addison-Wesley, Reading, pp.133–172.
- Klomegah, K.K. (2005) 'Russia counts cost of AIDS', *AEIGS (AIDS Education Global Information System)*, April 2005.
- Kushniruk, A.W. and Borycki, E.M. (2008) *Human, Social, and Organizational Aspects of Health Information Systems. Medical Information Science Reference*, IGI Publishers, Pennsylvania.
- Lyytinen, K. and Hirschheim, R. (1987) 'Information system failures: a survey and classification of the empirical literature', *Oxford surveys in Information Technology*, Vol. 4, pp.257–309.
- Mitnick, C., Bayona, J. and Palacios, E. (2003) 'Community based therapy for multidrug-resistant tuberculosis in Lima, Peru', *North England Journal of Medicine*, Vol. 348, pp.119–128.
- Nowak, D. (2006) 'AIDS spending will jump to 9M', *The Moscow Times*, 15 November 2006.
- Palella, F.J., Delaney, K.M., Moorman, A.C., Loveless, M.O., Fuhrer, J., Satten, G.A., Aschman, D.J. and Holmberg, S.D. (1998) 'Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators', *The New England Journal of Medicine*, Vol. 338, pp.853–860.
- Pouloudi, A. (1998) 'Stakeholder analysis in UK health interorganizational systems: the case of NHS net', in Andersen, K.V. (Eds): *EDI and Data Networking in the Public Sector: Governmental Action, Diffusion, and Impacts*, Kluwer Academic Publishers, Boston, pp.83–107.
- Power, D.J. (2002) *Decision Support Systems: Concepts and Resources for Managers*, Greenwood Publishing Group, Oxford.
- Ramnaryan, P. and Britto, J. (2002) 'Pediatric clinical decision support systems', *Archives of Disease in Childhood*, Vol. 87, pp.361–362.
- Ramnaryan, P., Cronje, N., Brown, R., Negus, R., Coode, B., Moss, P., Hassan, T., Hamer, W. and Britto, J. (2007) 'Validation of a diagnostic reminder system in emergency medicine: a multi-centre study', *Emergency Medicine Journal*, Vol. 24, pp.619–624.
- Rhodes, T., Lowndes, C. and Judd, A. (2002) 'Explosive spread and high prevalence of HIV infection among injecting drug users in Togliatti City, Russian Federation: implications for HIV prevention', *AIDS*, Vol. 16, pp.F25–F31.

- Rhodes, T., Sarang, A., Bobrik, A., Bobkov, E. and Platt, L. (2004) 'HIV transmission and HIV prevention associated with injecting drug use in the Russian Federation', *International Journal of Drug Policy*, Vol. 15, pp.1–16.
- Sarang, A., Stuikyte, R. and Bykov, R. (2007) 'Implementation of harm reduction in Central and Eastern Europe and Central Asia', *International Journal of Drug Policy*, Vol. 18, pp.129–135.
- Sargent, C. (2006) *Drug abusers ignored, untreated in AIDS epidemic*. Available online at: Bloomberg.com (accessed on 18 August 2006).
- Sauer, C. (1993) *Why Information Systems Fail: a Case Study Approach*, Alfred Waller, Henley-on-Thames.
- Schwalbe, N., Lazarus, J. and Adeyi, O. (2008) 'HIV/AIDS and tuberculosis control in post-Soviet Union countries', in Coker, R., Atun, R. and McKee, M. (Eds): *Health Systems and the Challenges of Communicable Diseases*, Mc Graw Hill, Maidenhead, pp.154–170.
- Senge, P.M. (1990) *The Fifth discipline. The Art and Practice of the Learning Organization*, Doubleday, New York.
- Sowadsky, R. (1999) *What is HTLV-III?* Available online at: <http://www.thebody.com/Forums/AIDS/safesex/Archive/origins/Q8777.html> (accessed on 24 August 2006).
- Sterman, J.D. (1989) 'Modeling management behavior: misperception of feedback in a dynamic decision making experiment', *Management Science*, Vol. 35, pp.321–339.
- Sterman, J.D. (2000) *Business Dynamics. Systems Thinking and Modeling for a Complex World*, Mc-Graw Hill/Irwin, Singapore.
- Tahaoglu, K., Torun, T. and Sevim, T. (2001) 'The treatment of multidrug-resistant tuberculosis in Turkey', *North England Journal of Medicine*, Vol. 345, pp.170–174.
- Tkatchenko-Schmidt, E., Renton, A., Gevorgyan, R., Davydenko, L. and Atun, R. (2008) 'Prevention of HIV/AIDS among drug users in Russia: opportunities and barriers to scaling-up of harm reduction programmes', *Health Policy*, Vol. 85, pp.162–171.
- UNAIDS (2004a) 'Report on the global AIDS epidemic 2004', *UNAIDS*, Vol. 48.
- UNAIDS (2004b) 'Report on the global AIDS epidemic 2004', *UNAIDS*, Vol. 52.
- Vajpayee, M., Kanswal, S., Seth, P., Wig, N. and Pandey, R.M. (2004) 'Tuberculosis infection in HIV infected Indian patients', *AIDS Patient Care*, Vol. 18, pp.209–213.
- Vynnycky, E. and Fine, P.E.M. (1999) 'Interpreting the decline in tuberculosis: the role of secular trends in effective contact', *International Journal of Epidemiology*, Vol. 28, pp.327–34.
- Wickramasinghe, N.S. and Goldberg, S. (2008) 'Facilitating superior chronic disease management through a knowledge-based systems development model', *International Journal of Electronic Healthcare*, Vol. 4, pp.299–310.
- Williams, B.G. and Dye, C. (2003) 'Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS', *Science*, Vol. 301, pp.1535–1537.
- World Health Organization (2003) *Global Tuberculosis Control: Surveillance, Planning and Financing*, WHO Report. WHO/CDS/TB/2003.316, Geneva, Switzerland. [www.who.int/gtb](http://www.who.int/gtb)
- World Health Organization (2005) *Treating 3 Million by 2005: Making it Happen: the WHO Strategy: the WHO and UNAIDS Global Initiative to Provide Antiretroviral Therapy to 3 Million People with HIV/AIDS in Developing Countries by the End of 2005*, World Health Organization, Geneva.
- World Health Organization (2007) *Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector*, World Health Organization, Geneva.
- Yadav, R., Sarasija, S., Kshama, D. and Yadav, S. (2009) 'Novel formulation of solid lipid microparticles of curcumin for anti-angiogenic and anti-inflammatory activity for optimization of therapy of inflammatory bowel disease', *Journal of Pharmacy and Pharmacology*, Vol. 61, pp.311–321.