RESEARCH ARTICLE OPEN ACCESS

A Blower-Like Approach to Predict the Effectiveness of Vaccines in a TB Dynamic

Carlos Frederico Fronza*[1], Janio Anselmo[1], Jefferson Luiz Brum Marques[1], Guilherme Brasil Pintarelli[1], Alexandre De Castro[2]
[1]Institute of Biomedical Engeneering – UFSC - Florianópolis, SC.
[2]Centro Nacional de Pesquisa Tecnológica em Informática para a Agricultura, Empresa Brasileira de Pesquisa Agropecuária - EMBRAPA

ABSTRACT
In this paper we present an extension of an automata approach proposed by S. Blower (1998) to describe the tuberculosis progression in a bi-dimensional space. In our extended model, the vaccination was included as an inhibitory variable in order to study its influence on the behavior of the tuberculosis spread. Our simulations showed that the earlier the vaccine is administered in the population, the lower the number of infected individuals, as expected for an in vivo system. However, our results also indicated that although the usual vaccination processes help reducing the strength of infection, the disease is not extinct, remaining the endemic state at low levels. These results strongly suggest that further actions are needed to increase the effectiveness of immunizations.
Keyword: Simulation, epidemic, tuberculosis, cellularautomata.

I. INTRODUCTION

Tuberculosis (TB) is an important health issue for Brasil and many others around the world. It is estimated that about one third of the world population is already infected with tuberculosis (Mtb). Each year 8.8 million new cases are reported [18]. TB is a disease that over the years has been concerning the world society, it has high risk of infection and contagion. A person infected is able to infect around 10 to 15 people over a period of one year [2]. The Mtb infection can be transmitted by coughing, sneezing, singing, speech, breathing, and even by tracheotomy individuals. This is a slow-developing disease, which in most cases occurs after two years after initial infection. The advent of vaccination with BCG and with increasing effectiveness of treatment reduced the chronic disease and its transmission in this community.

The treatments are in permanently evolution in past 50 years they were able to change the face of the disease appearance, move to the third age. The immunity occurs with the primary contact with the bacteria and vaccination, reduces susceptibility to infection, making the state of the population switch to the recover state, during until the immunity falls. Previous studies show that the immune response given by the vaccine in people already sensibilized by the Mtb from a primary infection does not bring an improvement in protection [19]. Some authors state that the main effect of BCG is to reduce disease progression more than the actual risk of infection (Smith et al. 2000). In order to help health services, indicating the crow of the disease, the advance in some neighborhood and indicate the epidemiological emergence, showing where it emerges, helping the decision making to becoming more dynamic to solve the potential problem. With this purpose was developed interdisciplinary urgent action, which has a bio-mathematical models and computer simulation dynamics. The idea of a dynamic model that is formed based on discrete time and consists of a spatial grid of cells filled in time and space [16]. In most cases, the classical models (SIS, SIRS or SEIRS) with transmission rate and population constant, present a unique endemic equilibrium. This paper shows the effectiveness of BCG vaccination in individuals of different age groups, studying the dynamics of tuberculosis in these people.

II. METODOLOGY.

In orderto developaprobabilisticcellular automata model, represented inacomputational grid where each cell representsanindividualandits location. This personisendowed withastatusthatgives itsplacein the dynamics. The epidemicdissemination can beconsideredas aset ofstatesdescribedas follows:Susceptible(hoping toget infected), latent(infected butwith the bacteriaunder control), Infected(bacteria activelytransmitsthedisease) Recovered(immune to disease) andifimmunityislowyou cango backto thestateSusceptible(when passinghasimmunityinsomecases) (SEIRS) [5]. Thediagramoftransition between statesis representedinFigure 1

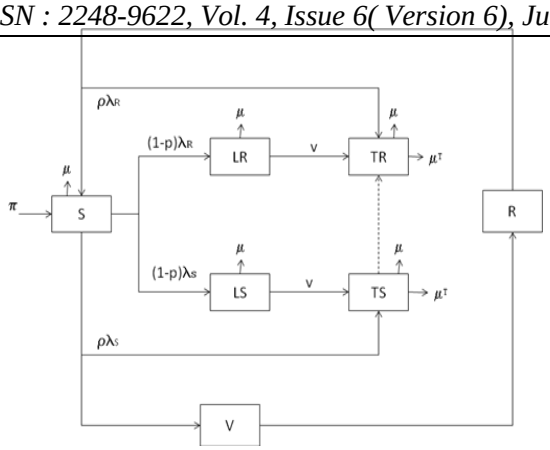

Figure 1: SEIR state model with vaccine, where □is the Power of infection, □is the recovery rate, □is the rate of infection and □is the mortality rate, is an adaptation of BLOWER, SM, 1998 model.
Source: BLOWER, SM, et all, 1998.

The main feature of the used model is the ability to develop locally. Since the tuberculosis bacillus needs necessarily of an direct and prolonged contact, since the disease develop slowly a concern should be taken in the model. The first infection may manifest in months or years. The global transmission exists, but is uncommon. For people from the same population, has the capacity of global transition is given by the total number of infected individuals in the network, due to their ability to walk (pG), is described by the equation:

ProbGlobal = Γ*(TS_Total + TR_Total)/N; where 0≤ ρ≤1 (1), where TS are the susceptible infected people, the TR are the resistant infected, the N is the total number of individuals in the grid and ΓandΛ are parameters used for small (forming clusters) and long distance (mean field) [9], knowing that pL>>pG.

To influence the population who lives around of a infected individual, local spread (pL), being its ability of infect given by the equation 2, where ProbTypeS is the probability to susceptible infected pass the illness:

- pL = 1.0 - (ProbTypeS + ProbTypeR - ProbTypeS*ProbTypeR). Where:
- ProbTypeS = 1.0 - pow(1.0 - lS, CountTS);
- ProbTypeR = 1.0 – pow (1.0 - LambdaR, (double)CountTR).

Wasusedto describe theindividualbehavior with his neighborhood theMooremodel, whereaperson is abletogetin contactwitheveryone around, the probalility ofinfection isgiven byequation2. Thedynamicsis givenas follows, the infectedindividualaccount the number of infected neighborsand look for the susceptible. From therewithacertain probabilitypL=1-(1-λ)^n, wherenisthenumber ofinfected individuals,passes intoa latent state.Withaprobabilityv,whichrepresentstime, socioeconomic,environmental and stateof immunity,the susceptible individualbecomesinfected, infectedaftertreatmentwelldone become recoveredclosingthechain.

III. RESULTS.

The simulations represented in this article demonstrate the TB behavior when submitted to interventions. The control parameters of bacilli spread were studied and taken from an mean of the Brasilian govern database and from others articles so the amounts should be approximate real life. The data simulated wore compared with the literature verifying the model efficacy.

In the figure 2 show that inspire of the vaccine has a significant importance for the primary tuberculosis prevention and some importance for pulmonary TB, the BCG is not able to put away the danger, letting the disease always at endemic state, only ranging the number of infected people. Was studied the vaccine in different levels of efficacy, 35%, 65% and 85%.When the efficacy of vaccine was putted at 90% of efficacy, but now was changed the time of shooting to: 1st, 10, 40, 80 years of the simulation, with or without the treatment or chemoprophylaxis. The results show that by increasing and decrease the efficiency, changing the date of the shooting not only decreases the level of infection, but also alter the life of the vaccine, how long protection lasts increases. Can be seen that the greater efficacy in vaccine and lower the age at which it applies the vaccine has a less variation between peaks and valleys, thus reducing the likelihood of an outbreak due to another event, such as opportunistic infections.

Once the vaccine is not only able to end the pathogen, the only way to eradicate the disease is thought the treatment, the treatment was used at a phi of 0.1 and 0.5 sigma, which are respectively the per capita rate of treatment and the rate per capita of chemoprophylaxis, used for third world countries, a number of treaties of 70% and 50% in chemoprevention, we studied with and without vaccine, 90% of the population were vaccinated and the vaccine efficiency was 85% and still dividing at ages of vaccination, 5 , 10, 20 and 50 it can be shown at the figure 1b.

The figure 3 show a treatment applied in some time after or before the year 5, 10, 20 and 50. This particular study shows that the disease is not completely, the epidemic wave drops, but the sickness continue in the endemic

way in low level. If vaccine is used perceives that the number of infected people levels drops even more but only when the shots are made between 0 and 5 years that the TB tends to disappear, but it doesn't. The figure shows too that if the vaccine is applied exactly at the first years, 0,1, 2, 3, 4 and 5 percent ofvaccinated people are greater than 85% and counting with a good treatment that's possible to exterminated the tuberculosis in the finite population.

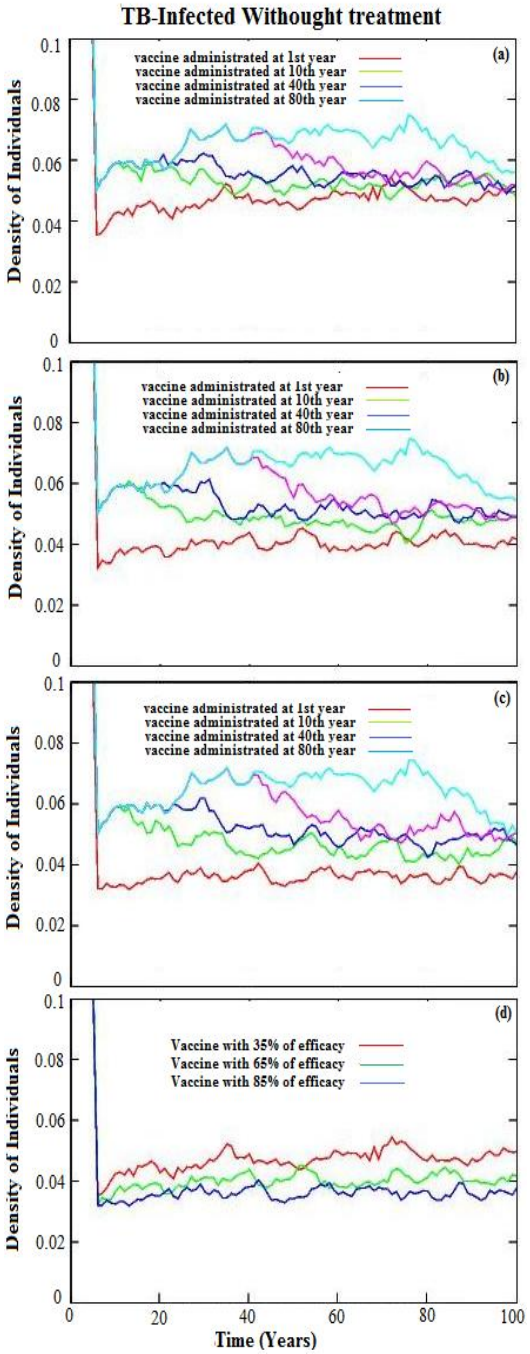

Figure 2 – Tuberculosis time evolution, (a) Vaccine with 35% of efficacy, administrated in the 1º ano, 10º ano, 40º ano e 80º ano. (b) Vaccine with 65% of efficacy, administrated in the 1º ano, 10º ano, 40º ano e 80º ano. (c) Vaccine with 85% efficacy, administrated in the 1º ano, 10º ano, 40º ano e 80º ano. (d) Show the contrast between the tree efficacy's at the first year.

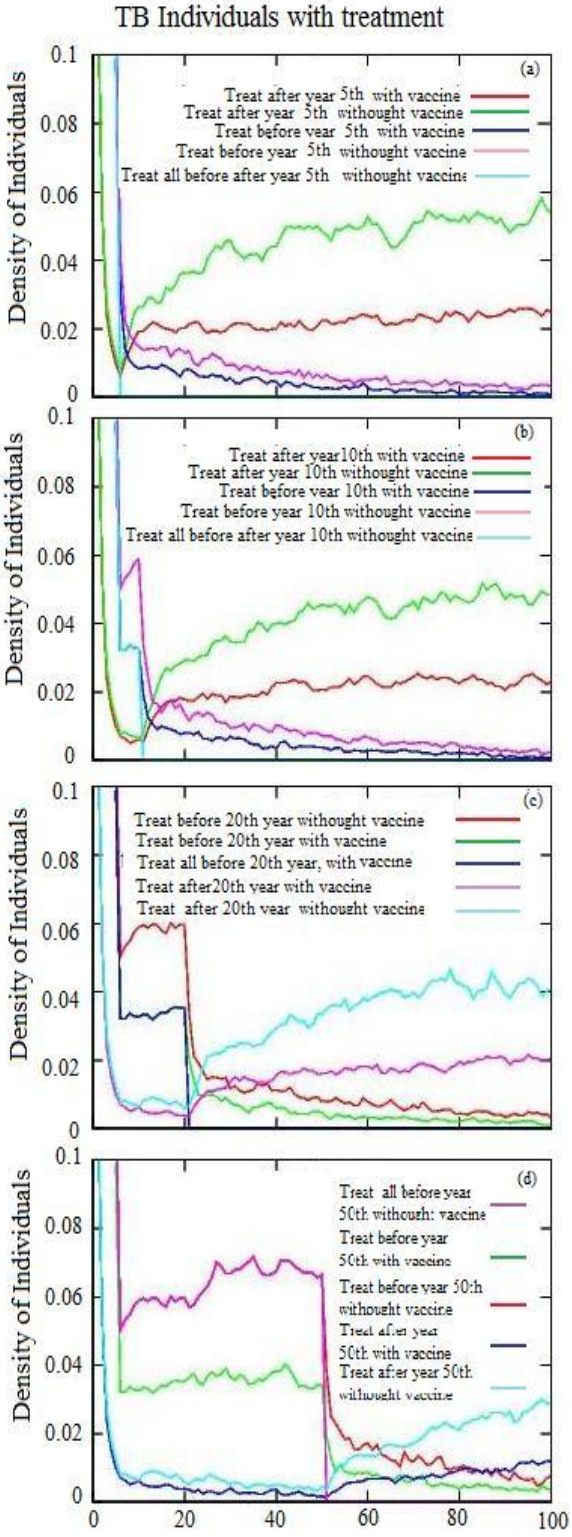

Figura 3 - Time evolution of tuberculosis, with a 90% percentage of vaccinated and 85% of vaccine efficacy. (a) Treatment in the 5th, the first 5 years and after 5 years, with or without vaccine. (b)

treatment in the 10th, the first 10 years and after 10 years, with or without vaccine. (c) Treatment at the 20th, the first 20 years and after 20 years, with or without vaccine. (d) Treatment at the 50th, the first 50 years and after 50 years, with or without vaccine.

IV. DISCUSSION

In the tuberculosis time behavior study, taking into account the age, gender and socioeconomic customs, this study aimed to verify the effectiveness of BCG as a prophylactic measure. By successive simulations using different vaccine efficacy, vaccinating at different ages and finally using the treatment. It can be seen that although the efficacy has a little influence on the performance of the disease, is able to reduce the force of infection, due to, once vaccinated the chances of getting infected diminishes.

Figure 1 focuses on the different rates of vaccine efficacy, 35%, 65% and 85%, with age vaccination, 1, 10, 40 and 80. The results shows that in the first year is was found the best immune response to vaccine. According to the Andersen study, vaccination of the newborn, which in our system represents the first year, is where the greatest relation age and vaccine efficacy (Andersen, 2007). So it was simulated for different efficiencies and different ages and finally settled the prime age, ranging only the vaccine's effectiveness. Thus it was realized that only with the variation in vaccine efficacy is not enough to achieved a significant improvement, the treatment is necessary to break down the disease cycle.

The finding is in agreement with the Andersen (2005), which questions the real effectiveness of the vaccine, showing that the protective performance of BCG decays with the coming years to maximum 10 to 20 years of protection. When dealing with efficacy of the vaccine in graph 2, it was explored between 35 and 85%, since there are reports suggest an efficacy of BCG for 0 to 80% (Pereira et al., 2007). BARRETO, (2006), reports that the power of BCG action varies from 0 to 86%, this variation may be caused due to the characteristics of the individual, their habitat, the strain of the bacillus among others. The finding that underscores the controversy about the efficacy of BCG, since there was no great difference in different efficacies after 85% (SUGAWARA et al, 2009).

Regarding vaccination coverage in this paper we used a coverage of 90% of individuals are vaccinated, this number varies with the environment, town and over the years in a given population. MIRANDA et al (1995) suggested that BCG vaccination coverage varies from 79 to 85%. MORAES et al (2003), reports that the coverage of BCG in the metropolitan region of Sao Paulo reaches 97.8%.

YOUNG, et al (2008) talks about the association between the BCG efficacy and the body's own ability to reject the disease without any intervention, since only 10% of the diseases manifests in its active form. In the same study was called into question the real effectiveness of the vaccine against pulmonary tuberculosis.

BIERRENBACH, et al. (2007) study is in agreement with the work proposed here, once the vaccine is applied the frequency of new cases of tuberculosis decrease mainly in the in the simulation first years, after some time the new cases of the disease start to grow back and If that is not properly treated, the disease itself stabilized and becomes endemic. However, with a high rate of infected people or the contraction of immune depressor sickness represents a major risk for the resurgence and possible development of an epidemic outbreak.

RUFINO (1977) reports that with at least 55.5% BCG efficacy it would be enough to keep the relationship economy – spending. According to the study proposed the vaccine is not able to replace the treatment, even with a 100% efficacy vaccine. In the literature can be seen that the efficacy of BCG varies from 50% to 87% (BARRETO, et al, 2006; SHEN, et al, 2008), it shows that the BCG that is produced today is not sufficient to snuff out the bacillus.

VASCONCELOS et al (2009) describes the ineffectiveness of BCG for preventing pulmonary TB, which is in agreement with our findings. However, the author reports on his study that in the process of developing a new vaccine against tuberculosis, which will be effective against secondary tuberculosis, would be a big step toward the end of tuberculosis.

However is possible to see in the result, in the first phase of tuberculosis plus the use of vaccine shows a substantial decline, this drop was already observed by ALMEIDA (1990) in his study that compared the mortality occurring in children under 1 year, before and after vaccine, showing that there is a regression from 7.9 times after the vaccine. This demonstrates that the protection afforded by the vaccine is in the first life age.

FU (2002) shows a historical evidence that in a population where individuals go through a network, either a city or a country, there is a chance that an infection after an outbreak will become endemic. Our findings corroborate this claim, since the tuberculosis disease always tends to be endemic in the state, according to the proposed model.

The figure 2 shows the endemic characteristic of tuberculosis, which remains throughout its existence, to looking at the figure 2 it's clear to see that the natural trend of tuberculosis over time is shown in linear average, this means that there are a outsized changes in its etiologic characteristic, unless something goes in advent that will strengthen the **Mycobacterium Tuberculosis** (Andersen, 2007).

The disease manifests as a tendency in many endemic countries, with a higher incidence in developing countries, that is the case of Brazil, affecting 10% to 15% of immunocompetent patients and 50% to 70% of individuals with acquired immunodeficiency syndrome (RIQUELME , 2006). By observing the second figure it is clear that **Mycobacterium tuberculosis** is no longer follow its natural tendency, stabilized, it can happen by feedback, genetic and environmental factors, the infection requires a long time relied on the bacterium, fee high virulence, and hostile conditions of life, which makes the transmission and spread, giving the human body able to make the first fight the disease (PENNA, 1988).

Tuberculosis is an injury that the environment itself gives man a natural vaccine, characterizing the stability of the disease without the presence of any adverse condition, the HIV can change the constancy of the disease and enhances the risk of developing active TB (KERR-BRIDGES, ET all., 1997). GLYNNA (1997) and Vasconcelos (2009), talk about how leprosy and HIV are considered extremely dangerous to be related to tuberculosis, are largely responsible for its appearance and / or resurgence, and that the combination of BCG vaccine in people with immunosuppression can be very dangerous. Confirming the hypothesis of this study in which only the associate diseases that depress the immune system are able to take the trend of endemic TB.

Figure 1 shows the trend of tuberculosis in time for a vaccinated population in year 1, 10, 20, 40 and 80, with an efficiency of 35%. The choice of vaccine efficacy for this experiment was made because is a low percentage, and it is in agreement with the variation of effectiveness according with (PEREIRA et al., 2007). With an effective so low it is clear that the spread and stabilization, are not much different for all ages. In the first years of life, 0 to 5 years, can be observed the highest percentage of BCG effectiveness, 84%, making the choice of one year as the key year for the best use of the drug. The variation in vaccine efficacy also suggests the age difference in a population where the highest efficiency is obtained in the first five years of life with a protection given to 85% to 87%, however over the years the protective effect decreases.

Over the years as seen in the figure 2 the effectiveness begins to decrease, which leads us to choose the 10th year since between the ages, 1 and 15 years the BCG efficacy drops about 59%, proving what was suggested in the resuts (Barreto et all, 2006). In this trend the vaccine administrated in the years 20 and 40 shows a higher degradation in its protective effect, combined with the worst habits of life of a young population, cases of tuberculosis increasing in this age group. From the age of 50 despite the older population better watch out, your body, the defense no longer works as before, their effectiveness drops to lowest index to measure the mortality rate increases, Wales (1998), discusses the growth of the adults deaths for young people between 20 and 49, representing 59.7% of deaths and the decline in deaths to less than 20 and greater than 50 years.

SHEN et al (2008) presents in his paper that not only has the vaccine more effectiveness when younger, but also the duration of its protective effect last longer, as suggested in the paper. The attenuation of immunity caused by BCG, decays with time as evidenced by this hypothesis DOHERTY (2005) that shows even with the continued reduction of the protective effect conferred by BCG vaccination compromises the body ability to stimulate production of antibodies and immune memory.

The treatment is taken as the only way to really remove the bacillus of the human body system, but only with a treatment well done from start to finish. Jasmer et al (2004), describes in his article that treatment well made, properly led from the beginning to the end represents a healing capacity of over 97.5% of cases and also alerts on the problem of treatment abandonment which gives strength to the **mycobacterium tuberculosis** making it more resistant and difficult to treat. VALLEJO (1994) calls attention to the fact that if the treatment is done correctly and has sooner start it can be a cure in about six months, explaining the sharp drop shown in figure 3 where the processing is done with efficiency and accuracy.

The figure 2 shows the tuberculosis in time with and without vaccine, at the ages already mentioned in this discussion, but at this time was add the treatment as well. As seen in this work the BCG is not able to suppress the bacillus, so the treatment is necessary to cease the illness, since only effective treatment is able to eliminated it (Andersen, 2005). The figure portrays the treatment of individuals, minor and equal to 5 years old, using the fifth year as reference. In this discussion it was resolute that at the ages 0-5 is where can get the best results for contraceptive measures. Was also used in this simulation the treatment well done and ineffective treatment, a treatment that was not completed, the incomplete treatment reflects a major problem for public health, since the bacillus becomes resistant to drugs (LIMA et al, 2001).

The settled treatment on the year fifth can be called an early treatment, as it is done in children has a good adhesion, making it the fastest and safest treatment (LIMA et al, 2001; Perreira et al, 2007). It can be seen that within an increasing age makes the treatment with or without vaccine, with a well done treatment, ruled at any age the real improvement occurs. The vaccine can help a bad treatment,

however it appears an increase of infected individuals resistant.

In his study Koriki (2008) reports that at the equilibrium, endemic, the tuberculosis is able to change your state depending on external conditions, as associated diseases, differences in climate, inhospitable regions, as well as the population socioeconomic level. This information goes in agreement with was showed on the results obtained in this work. In its endemic form, the infection only can become active with a disturbance in the disease routine.

V. CONCLUSION.

The proposed model was used to aid and check the decision making regarding to the epidemiology of tuberculosis. The results showed in this paper were satisfactory and from them we can infer that:

- The BCG has great accuracy and effectiveness for populations of individuals between the ages 0 to 5 years. After this age the vaccine's effectiveness begins to wane.
- The vaccine is not able to influence the spread of pulmonary tuberculosis, showing that BCG is the way you made today has a positive effect, ending only with severe forms of primary tuberculosis.
- Since the vaccine reduces slightly the amount of infected individuals in the network, the treatment is necessary, only the treatment is done properly able to shoot with tuberculosis.
- Poor treatment generates dangerous consequences, makes the multi resistant bacillus. The above study did not focus on MDR, but future work will be given greater attention to this issue.

This study is very important to create a discussion, since it will provide a different perspective and depth on the observed behavior of the disease in question. The results of the works show the reality of tuberculosis in Brazil as well as their way of life, this indicates that the model can be used to simulate the behavior of many tuberculosis situation satisfactorily. This way you can monitor and study the TB from the proposed system.

BIBLIOGRAPHY

[1] ANDERSEN, P; DOHERTY.***The success and failure of BCG implications for a novel tuberculosis vaccine*.**Nature, 662, vol. 3, august, 2005.

[2] ANDERSEN, P. **Tuberculosis vaccines** — *an update*, Nature 2007 v-5.

[3] BARRETO, M.L; PEREIRA, S.M; FERREIRA, A.A. BCG vaccine: ***efficacy and indications for vaccination and revaccination***. Journal of Pediatrics, 3, vol 82, 2006.

[4] BLOWER, S; PORCO, T..***Quantifying the intrinsic transmission dynamics of tuberculosis***.Theorical Population Biology: 1998,v 54: 117–132.

[5] BLOWER, S; ZIV, E; DALEY, C.**Early therapy for latent tuberculosis infection**. American Journal of Epidemiology 153 (2001), 381–385.

[6] JASMER, RM; SEAMAN CB; GONZALEZ, LC; KAWAMURA, LM; OSMOND DH; DALEY CL. **Tuberculosis *Treatment Outcomes Directly Observed Therapy Compared with Self-Administered Therapy*.** Am J RespirCrit Care Med Vol 170. pp 561–566, 2004

[7] KORIKO, OK; Yusuf, TT. *Mathematical Model to Simulate Tuberculosis Disease Population Dynamics.*American Journal of Applied Sciences 5 (4): 301-306, 2008

[8] LIMA, MB.; MELLO, D.;A MORAIS APP.; SILVA, WC. Estudo de casos sobre abandono do tratamento da tuberculose: avaliação do atendimento, percepção e conhecimentos sobre a doença na perspectiva dos clientes (Fortaleza, Ceará, Brasil). Cad. Saúde Pública, Rio de Janeiro, 17(4):877-885, jul-ago, 2001

[9] PEREIRA, SM.; DANTAS, OMS,; XIMENES, R.; BARRETO, ML. *Vacina BCG contra tuberculose:efeito protetor e políticas de vacinação.*Rev Saúde Pública 2007;41(Supl. 1):59-66

[10] SHEN, H; HUANG, H; WANG, J.S.YE; LI, W; WANG, K; ZHANG, G; WANG P.

[11] ***Neonatal vaccination with Bacillus Calmette-Gue´rin elicits long-term protection in mouse-allergic responses***. Allergy 63: 555–563, 2008.

[12] **VALLEJO JG; ONG, LTPA-C; STARKE, JR.Clinical *Features, Diagnosis, and Treatment of Tuberculosis in Infants.****Pediatrics.*1994; 94: 1-7.

[13] YOUNG, DB; PERKINS, MD; DUNCAN, K; BARRY III, CE.***Confronting the scientific obstacles to global control of tuberculosis.****J. Clin. Invest.* **118**:1255–1265, 2008.