Tuberculosis - Epidemiology and Control Issues in Global Perspective

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Although being one of the most thoroughly studied diseases in epidemiology, tuberculosis (TB) is now re-emerging with quite new epidemiological characteristics, such as TB combined with HIV infection, and multiple-drug resistance TB. These new aspects can add very serious impact on the existing health burden of TB, especially its serious inequality between developed and developing parts of the world in demographic, social and economic terms. These epidemiological aspects of TB problem will be illustrated in a stepwise way, using several mathematical models. The application of epidemic model of TB is also shown for evaluation of some TB control measures. J Epidemiol, 1996; 6: S57-S63.

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Tuberculosis is considered to be one of the most thoroughly studied problems in epidemiology. However, it is now re-emerging with new epidemiological characteristics in addition to its classic features. Tuberculosis combined with HIV infection presents with a very unique natural history, from infection through clinical breakdown and progression. Multiple-drug resistant tuberculosis is another formidable and foreign problem. Thus, tuberculosis is challenging us in new ways, in both developed and developing countries toward the end of the 20th century in spite of the optimism of the 1960s and 1970s. In this brief lecture I would like to put the problems of tuberculosis in an epidemiological perspective, using mainly epidemiological models.

A Simple Epidemiological Model and Simulation of the Secular Trend of Epidemics

Figure 1 illustrates the mechanism of tuberculosis in a human population in a very simple way. Suppose we have 100 persons who have been infected with tubercle bacilli. They are observed lifelong for clinical development of tuberculosis. It is estimated that roughly 10% of them may develop smear-positive tuberculosis at varying times. The patients are then observed with no intervention to see if they die or are cured, hypothetically, on average after two years. During these two years they remain active as sources of infection. We assume that one source of infection can infect five persons over a year's time. So, because we have 10 cases, each active for two years, we can expect 10 x 2 x 5 = 100 new infections from this group of patients. Having started with one hundred infected, we have now gone a full cycle and are left with another 100 infections, which in turn are the start of a new cycle.

In a population where the values of the indicators, or the parameters for clinical breakdown, disease duration, and contagion are set as above, the tuberculosis situation will be forever constant, every one hundred infected persons producing 100 new infections from this group of patients. Having started with one hundred infected, we have now gone a full cycle and are left with another 100 infections, which in turn are the start of a new cycle.

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After the cycle we will have only 64 infections, and then 51, 41, 33, and so on. In this way, the epidemic’s extent will diminish gradually given a reduced value of any of the parameters. However, the tuberculosis situation will deteriorate if something occurs which increases the value of any of the parameters. Apparent improvement or worsening of the situation, as seen in the history of tuberculosis in many countries during the progress of industrial revolution, wars, or economic development, may be the result of a readjustment of the parameter values, as illustrated above.

It is easy to simulate using this model the changes in tuberculosis epidemics in terms of the number of new cases produced or the number of new infections, under conditions elevating or reducing the rate of reproduction due to a change in, for instance, the risk of clinical breakdown, duration of disease, or contagion. A change in these parameter values results in a continuous reduction or increase of tuberculosis epidemics. In the secular trend of tuberculosis mortality in England and Wales since the beginning of the century, it is observed that the rate of reduction during 1900 and 1945 was about 2.6% per year, and 13% per year after the war. It is supposed that before the war the gradual improvement in socioeconomic conditions and nutrition had the effect of reducing the parameter values to that extent, and that the post-war introduction of modern tuberculosis control measures was more effective than that. Although model I showed is a very simple example, it may be sufficient to simulate the basic trend of tuberculosis.

**Annual Risk of Infection as a Parameter for Epidemiological Problems**

Examining the amount of infections in a more realistic way, we can introduce the idea of risk of infection, i.e., the chance of an uninfected person becoming infected during a year. This parameter is intended to express the epidemiological size of the tuberculosis problem. Figure 2 shows the trend of annual risk of infection for the Netherlands \(^1\), known to currently have the world’s lowest risk, and that of Japan, where the risk is far higher than in the Netherlands \(^2\). Many industrialized countries have a risk of infection at levels below 0.3%; Korea and other countries with newly industrialized economies are approaching this level or are below it. Many developing countries still remain at a level of 0.3% or higher, and their trend is only slowly downward, at a standstill, or even upward.

The annual risk of infection can be measured rather easily based on the tuberculin survey results. One useful element is that there is a rough relationship between the annual risk of infection and the incidence of active tuberculosis in high prevalence areas such as developing countries, i.e., 1% of the risk of infection corresponds to an incidence rate of 50 per 100,000 \(^3\). Based on this assumption, researchers of WHO and CDC of the USA estimated the burden of tuberculosis in developing areas, in terms of tuberculosis incidence (which is generally difficult to obtain) for the respective regions of the world \(^4\). Obviously, tuberculosis presents a notable inequality of health which is unfavorable to developing countries. About 95% of new tuberculosis cases and 98.5% of tuberculosis
It is well known that tuberculosis is very dependent on age in many ways. Therefore, the simple model you have seen is not adequate for simulating tuberculosis dynamics in a realistic way. For this purpose, Waaler developed a mathematical model in the 1960s, as shown in Figure 3. This is one of the pioneering works in this field, and Waaler conducted many other studies.
studies using it, including early works involving a cost-effectiveness analysis of a tuberculosis control program. In Japan, Endo and Aoki are the first to conduct epidemiometric model studies and cost-effectiveness analyses using this model. Later Mori applied this model for the risk-effectiveness analysis of the radiophotography service for screening of tuberculosis in the Japanese population.

In the model, the population is divided into 8 subgroups, each combined with epidemiological relations or flows. This set of subgroups and flows are assumed for every 5-year age group, with age-specific parameter values for corresponding age groups.

As an illustration of the output of this model, I produced an age-specific incidence rate for successive years for a fictitious low prevalence population (Figure 4). As you see, the incidence peak shifts to the right, along with a downward trend of tuberculosis for all ages, reflecting the well-known cohort phenomenon. In this way, the model incorporates the age-specific aspects of tuberculosis epidemics.

Quality of Tuberculosis Model in Developed vs. Developing Countries

Here, apart from the model, I would like to examine this aspect of the global tuberculosis problem. The age-specific prevalence rates of tuberculosis infection in Japan for 1950 and 1990 were estimated from the trend of annual risk of infection as seen above. The tuberculosis situation in Japan in 1950 was that of the high prevalence area now. The comparison between these two situations is clear - in a high prevalence situation, the prevalence is already high for young persons, while in a low prevalence situation it is very low for the young, but considerably high for older persons, the latter reflecting the high infection risk in their past. By applying the age compositions of developed and developing countries to this infection curve, the age-composition of the infected persons in a population is obtained that is striking, as seen in the comparison between the USA and Tanzania. In a low prevalence situation such as the USA, about 93% of the infected persons are aged 40 years or more, while in a high prevalence situation only 35% are so.

Disease Control Priorities Based on DALY

This difference in age-composition results in a remarkable difference in the age patterns of patients tuberculosis which developed from infected persons. The higher risk of clinical breakdown in adolescence also operates in producing this age pattern. In a low prevalence area, e.g. the USA 54% of the cases are 55 years or older, while in a high prevalence area such as Tanzania only 18% are of that age, which indicates that in a high prevalence area tuberculosis occurs in economically and socially active segments of the population, affecting society and households. The same may be true for the tuberculosis burden due to deaths. Thus, we should consider whether the tuberculosis problem is somewhat underestimated when it is evaluated only in terms of the number of deaths or new

Figure 4. Simulation of the Cohort Phenomenon (Fictitious population, Incidence Rate)
cases. Recently, trials have been done to measure the disease burden more equitably, by giving weight to losses due to disease in the young. This approach is called DALY, or disability adjusted life years, and is used by WHO and the World Bank as one basis for disease control priorities. In a series of works, loss of DALYs due to death and illness or disability caused by various diseases, and also the DALYs to be saved with unit of money for the disease control program are compared. The results of these works are claimed to be a more relevant basis for priority in investment in the health sector. As a conclusion, tuberculosis is shown to be underestimated in the health policy in the developing world, by both the donor and recipient government, when the investment in the tuberculosis control program is more rewarding.

**Evaluation of Treatment Program**

Getting back to the Waaler model, the model is used to predict situations under various tuberculosis control programs, where the effect of each of the control measures is expressed as a modified parameter value of the relevant flows. The results of the simulation of case-finding and treatment at various intensities are shown in Figure 5. For example, when the case-finding and treatment program is introduced at time zero and maintained after that, then the number of new cases may take a course like this over time. This kind of prediction of fictitious situations using a model enables the rational evaluation of a control program.

In the original Waaler model, the emergence of chronic bacillary cases and drug resistant tuberculosis cases resulting from treatment failure is not incorporated. In the face of this new problem, which is prevalent both in developing and developed countries, a refinement was made to the model in order to compare the outcomes of treatment programs with higher and lower treatment success rates. The cost-effectiveness analysis was made to compare the treatment regimens of short-course chemotherapy that required the more expensive medications for 6-8 months, and the standard chemotherapy using cheaper medications for at least 12 months, both with and without hospitalization, with the use of a model based on the above principle to simulate the clinical course of tuberculosis patients. Apparently very expensive short-course chemotherapy may pay off fairly well in comparison with the nominally cheap standard regimen, in terms of cure, death aversion, and life years saved. This analysis result is the basis of WHO's policy to recommend to developing countries the use of well managed short-course chemotherapy, now called the “DOTS”, Directly Observed Therapy, short course.

**The Impact of HIV Epidemics on Tuberculosis**

The epidemic of HIV and its impact on tuberculosis, first
noted in the USA, presents a problem far more serious in developing countries, especially in sub-Saharan Africa and some parts of Asia. From early observations in the USA and Africa, it was easy to predict the very serious impact of HIV/AIDS on tuberculosis. The Waaler model was refined so that each subgroup has HIV components, including seronegative, positive, and AIDS status. In this model the HIV transmission is to be determined externally. Test runs of the model, with some uncertain parameter values, generated the results shown in Figure 6; when HIV spreads at 1% per year, the prevalence of tuberculosis increases very steeply. This is very similar to the actual observation from some African countries. The effectiveness of tuberculosis control measures, such as good case-finding and treatment, and chemoprophylaxis, is simulated in this way. But the benefit of such measures is quite limited. WHO and CDC made a future prediction of the HIV-impact on tuberculosis. The gloomy worldwide situation will be aggravated in the near future due to the spread of HIV infection, mainly to Asian countries. According to the estimate, in 1990 HIV accounted for 5% of newly-occurring cases globally, which will be 14% by the year 2000. In southeast Asia, the HIV-attributable risk was only 2% in 1990, but it will be 15% in 2000. The "tuberculosis explosion" in Asia may be already beginning in Northern Thailand.

In the above presentation I have attempted to show the usefulness of an epidemiological model to describe the global situation and problem of tuberculosis and the decision making of its control policy and program, not necessarily in a very systematic way. Taking into account reservations regarding possible limitations and pitfalls, the models can be and should be utilized more widely, and recent advances in computer hardware, as well as software, will make it a more epidemiologist-friendly technology.

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