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ANNUAL RISK OF TUBERCULOUS INFECTION*

by

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I. INTRODUCTION

Risk of infection in a population is in many respects the most informative index of the magnitude of the tuberculosis problem (Sutherland, 1976; Pio, 1984). The risk of infection at a particular time indicates the current magnitude of the incidence and prevalence of infectious cases (Styblo, 1985) and also indicates the magnitude of the tuberculosis problem years into the future. An observed decline in the risk of infection would be the earliest indicator of a decline in the epidemic cycle of tuberculosis, resulting from tuberculosis control activities or improvements in living standards. A rising risk of infection would be an early indicator of changes in the other direction, signalling the introduction of new risk factors, such as the spread of human immunodeficiency virus (HIV) infection.

It is known that risk of infection has been declining for many years in developed countries, but remains at high levels in many developing countries (Styblo, 1984). In developing countries in the last decade, a number of surveys of infection prevalence have been carried out in national populations as well as in smaller populations.

Therefore a project was carried out to assess the current level and trend in the risk of infection in developing countries by reviewing and assembling tuberculin skin test survey data available since 1975.

II. METHODS

Tuberculin skin test data collected since 1975 for populations in developing countries were assembled from reports to the World Health Organization and from the published literature. Data from surveys of childhood age groups that were judged of sufficient quality were selected in order to provide as valid and up to date an assessment as practical of the magnitude of the risk of infection. Comparable prior data for the same countries were also selected in order to judge whether the risk of infection is likely to have declined.

Prevalence of infection observed in childhood age groups was used to derive the average annual risk of infection that would have resulted in the observed cumulative prevalence rate. Choosing younger age groups allows the calculated average annual risk to be bracketed within a relatively narrow period of time between the average birth date of the group and the date of the survey (Styblo et al, 1969).

Each survey was judged on the basis of available documentation for ability to represent the population and to detect the proportion infected at a particular time. A sample survey was judged to have measured the proportion infected in the target population if the probability sampling design and the estimation method appeared correct in concept and conduct, and skin testing technique appeared adequate to measure the proportion infected in the sampling units.

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Basis for selection

Surveys were selected which met most of the following criteria:

Specified the sampling design including the sampling frame, staging, stratification, sampling units, allocation, sampling weights, and estimation formulas and documentation to support that the design was followed with adequate coverage.

Provided reaction-size distributions for surveyed age groups and for bacteriologically confirmed cases from the same population in order to assess the definition of infection and in order to judge technique.

Documented type and strength of antigen used, technique of administration and reading, and quality control procedures.

Specified the methods used to detect and eliminate persons with a history of BCG vaccination, and described BCG policy and actual coverage in the population age group surveyed.

Data assembled from selected surveys:

The area population represented and the survey period.

In the youngest age ranges for which sufficient numbers were tested and read, the number tested and read, the number counted as infected with M. tuberculosis, and the mean age.

Information documenting quality of the data.

Criterion of infection

Induration reaction size distributions observed in each survey were used together with general knowledge about the specific and nonspecific components of observable distributions to set a uniform criterion for counting infected persons in order to improve comparablility between surveys.

Because it can be assumed that nonspecific reactions to intermediate strength purified protein derivative tuberculins are only infrequently larger than the mode of the distribution of true reactions, an observed distribution of tuberculin reactions will be nearly free of contamination by nonspecific reactions above its mode.

Because of this, and because distributions among truly infected persons are symmetric, the number truly infected in a distribution contaminated by nonspecific reactions would be closely approximated by adding the number at the mode plus twice the number with reactions larger than the mode.

This method, described by Nyboe (1960) and by Comstock et al. (1971), was used to determine the number of infected persons in the selected groups when detailed reaction size distributions were available and when the mode of reactions among infected persons in the same general population could be estimated from distributions of either bacteriologically confirmed cases or older age groups in the population.

When such data were not available, a cutoff criterion was accepted as the second choice if it appeared reasonably adequate based on distribution data.

Prevalence

Prevalence at a particular calendar time for an age group was calculated as the number infected divided by the number tested and read. Reported prevalence figures were used when numerator or denominator counts were not specified.

Risk of infection

For comparability, a single uniform method was chosen to derive the approximate average annual risk of infection (Styblo et al, 1969, pg. 14). By this method, the annual risk of infection (R) for a group of average age (A) was derived from the prevalence (P) by

$$R = 1 - (1 - P)^{1/A}.$$

The slope per year (B) of the trend between two risk estimates R_i and R_j at years Y_i and Y_j was approximated by

$$B = 1 - (R_j/R_i)^{1/T} \quad \text{where } T = Y_j - Y_i.$$

Average age

Average age was calculated by taking the midpoint of a single year (e.g., 6.5 for age given as 6 at last birthday) or a range of years (e.g., 7.0 for ages given as 6 to 7, or 7.5 for ages given as 5 to 9). When available, the weighted average age was calculated from year-of-age specific frequencies for an age group.

Time at which average risk occurred

For purposes of calculating and plotting trends, the calendar time of occurrence of a particular average annual risk (Y_R) was considered to center approximately at the calendar time of the midpoint of the average lives of the individuals in the age-group. This was calculated by $Y_R = Y_S - A/2$, where A is the average age of the group and Y_S is the midpoint time of the survey. For example, a group of average age 6.1 years surveyed at 1978.9 was taken to contribute information about the annual risk of infection for a time interval centered at 1978.9 - 6.1/2 = 1975.85.

The midpoint time of the survey (Y_S) was calculated from the month, if stated, or the calendar year of the survey. For example, a survey stated to have taken place in 1975 was counted as occurring at 1975.5. A survey stated to have taken place from 1981 to 1982 was counted as occurring at 1982.0. A survey stated to have taken place from May 1952 to September 1953 was counted as occurring at 1953.04 (the midpoint between 4.5/12 + 1952 and 8.5/12 + 1953).

III. RESULTS

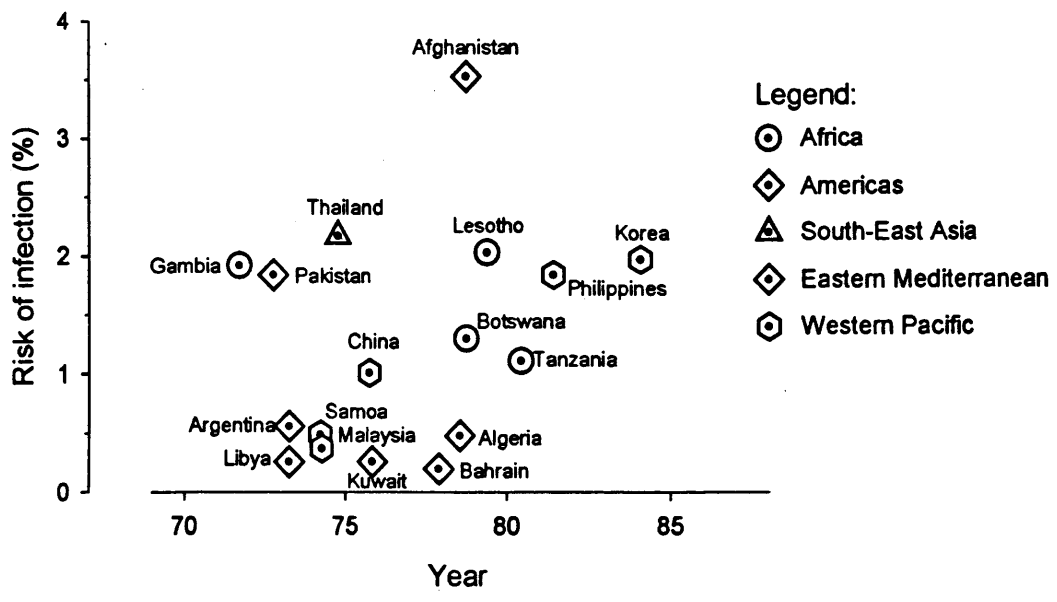
A variety of tuberculin skin-test surveys were found in the published and unpublished literature: National sample surveys, sample surveys of other large populations, school surveys, school BCG campaigns, and mass BCG campaigns.

Twenty-five countries were judged for the purposes of this project to have been adequately surveyed in whole or significant part since 1975.

Figures 1 and 2 display the results for each country by region. Table 1 contains the data used in the figures and describes the area population represented, the survey design, the level of BCG coverage in the age-group surveyed, and the antigen and criterion defining infection.

An arithmetic scale is used in Figure 1 in order to display the relative magnitudes of current estimates of annual risk of infection.

Fig. 1. **Annual risk of tuberculous infection in low-income countries of five WHO regions**



A logarithmic scale of annual risks is used in Figure 2 in order to represent constant percentage decreases or increases between current estimates and prior estimates as straight line trends.

Dark symbols in the figures indicate risk estimates based on 42 well-conducted national sample surveys in 16 countries. In Figure 2, dark solid lines are used to connect rates which are based on more than one large sample survey of the same country.

Light symbols in Figure 2 indicate risk estimates based on data representative of lesser populations.

Dark dashed lines in Figure 2 are used to connect risk estimates based on national sample survey data with risk estimates based on other substantial data such as tuberculin testing in the mass BCG campaigns. A light solid line was used to connect risk estimates from repeated surveys representative of lesser populations. A light dashed line was used to connect surveys of approximately the same population done in different years.

The symbol + was used in Figure 2 to indicate the average of a set of risk estimates which together would represent a larger population. Stratum estimates within sample surveys, plotted as separate points to reveal variation in risk, were displayed as a single estimate for the whole population in this way. Sets of small area estimates that were less representative of the whole population than would have been provided by formal probability sampling, such as the set of completed sampling units in a not yet completed national survey, or areas selected by judgement from geographic or economic strata in order to be representative of a large heterogenous population, were also combined in this way.

To indicate the extent of underlying variability, risk estimates from single surveys that were representative of only small areas are indicated in Figure 2 by unconnected light symbols.

Results by region

Africa. The most recent data for the eight countries included indicate current annual risks of infection around 1 to 2 percent. In the five countries for which comparable earlier surveys were available, trends over 20 to 25 years appear to be downward at 1 to 6 percent a year.

Data for the nearly completed national survey of Tanzania indicate an annual risk of infection of 1.1 percent, based on a population weighted average pooling of the samples. However, comparisons with earlier data available for three of the 18 regions in the sample do not together suggest a downward trend.

Surveys in Botswana and Lesotho suggest downward trends of about 6 and 1 percent a year, respectively. In the most recent survey in Botswana, however, BCG coverage in the age group surveyed had reached 83 percent, leaving only 17 percent who had by whatever circumstance missed vaccination, upon which to base the estimate.

No national surveys were available for Cameroon, but two surveys of the capital city, Yaounde, were available. These surveys indicate a level of annual risk of 0.6 percent in 1980 after a 20-year declining trend of 3.6 percent a year.

Survey data collected 30 years apart were available for Addis Ababa, the capital city of Ethiopia. These surveys indicate a 1.3 percent level of annual risk in 1979 succeeding a downward trend of 3.7 percent a year from the 4.1 percent risk level in 1949. A survey of selected villages in the Southwest, however, indicated a 3.8 percent annual infection risk in 1973. This suggests that within Ethiopia there is large variability in the level and perhaps also in the trend of infection risk.

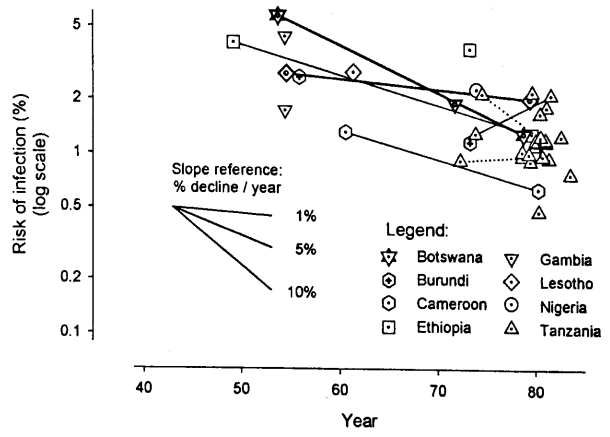
Data from the 1976 sample survey of Gambia indicates an annual risk in 1971 of 1.9 percent. The trend of risk could not be assessed in Gambia, however. The only prior data available are from the 1958-59 survey of the capital city, Bathurst. The annual risk of infection in the urban stratum (4.4 percent) was higher than in the rural stratum (1.7 percent), which was nearly the same as the national level in 1971.

The annual risk of infection derived from skin test data for all military recruits in Burundi in 1981-82 was 1.2 percent. Data from an earlier survey among a scattered provincial population were selected in order to provide a rough comparison. The annual risk of infection in that group was 2.7 percent in 1955.

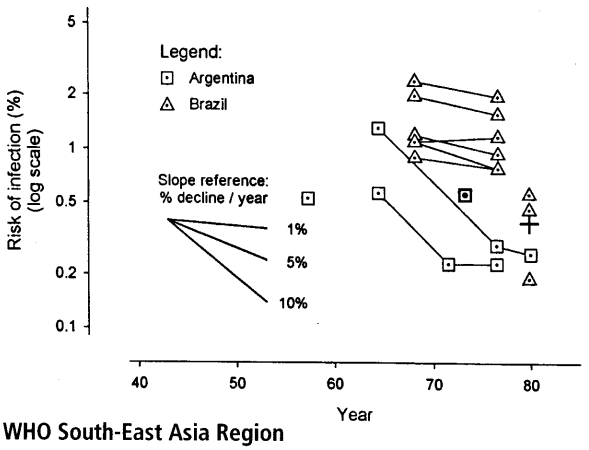
No comprehensive survey of the Nigerian population was available, but data from a survey of one emirate indicates an annual risk of 2.3 percent in 1973.

Fig. 2. **Annual risk of tuberculous infection**

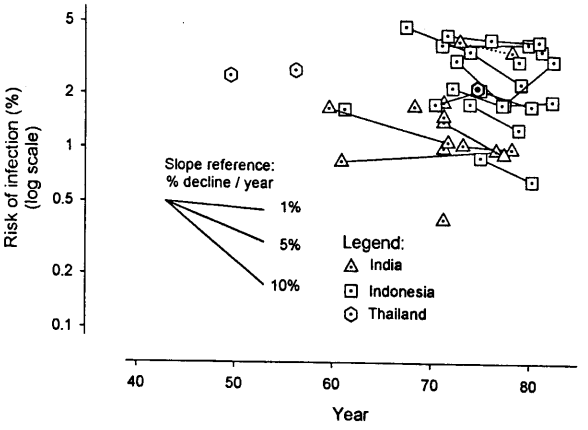
I WHO African Region (except Algeria)



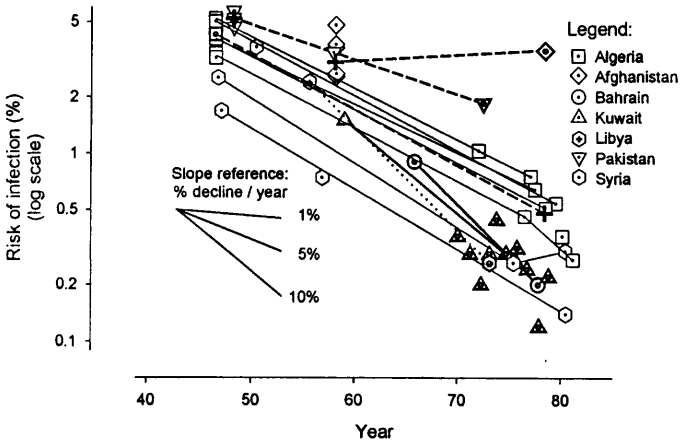
II WHO Region of the Americas



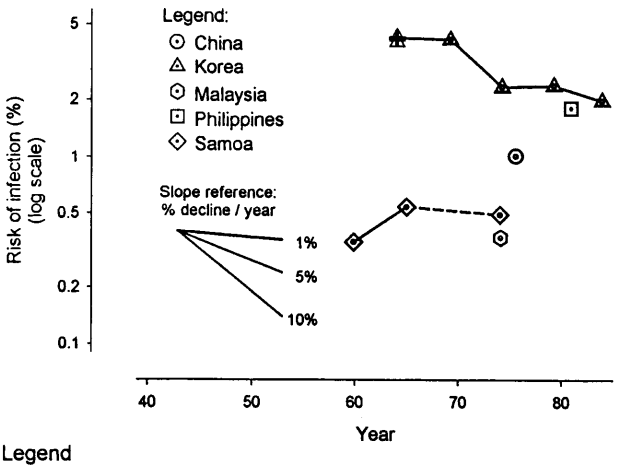
III WHO South-East Asia Region



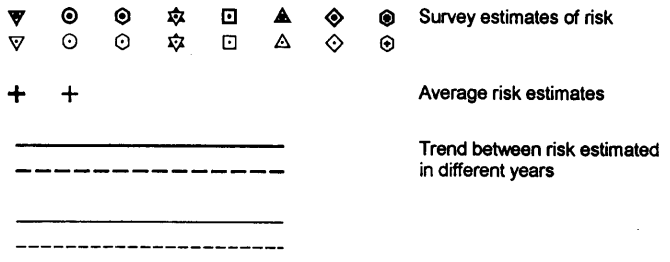
IV WHO Eastern Mediterranean Region



V WHO Western Pacific Region



Legend



Dark symbols and lines are used to display risk estimates and trends for national populations and large parts of national populations.

Light symbols and lines are used to display risk estimates for subnational units.

Solid lines connect surveys that closely represent the same population.
Dashed lines connect surveys that represent approximately the same population.

Americas. National sample survey data were available only from Argentina, but repeated surveys of large local populations within Argentina and also within Brazil were available. In the latest surveys, infection risks in these local populations varied ten-fold from 0.2 to 2 percent per year. Over time in these local populations, there was evidence of a steep decline in risk in Argentina, and a lesser decline in Brazil.

The annual risk of infection derived from the 1974-78 survey of the entire population of Argentina was 0.6 percent. Data from three surveys repeated in Santa Fe City and three surveys repeated in areas around Santa Fe City indicate low recent levels in that region of 0.2 to 0.3 percent annual risk, and indicate that the trend of the previous 12 to 15 years was steeply downward at a rate of 7 to 10 percent a year. The two trends described by the two sets of three survey points suggest that the decline was much steeper between the first two surveys but that the trend was nearly level during the 5 years between the second and third surveys. In the 1960-61 sample survey of another area of Argentina, Resistencia Province, the annual risk of infection was 0.5 percent.

Capitals of Brazilian States and Territories were surveyed in 1970-73 and again in 1980. The annual risk of infection was 0.8 to 1.9 percent in 1976 with evidence of a yearly downward trend of around 2 to 3 percent. A 1983 survey of the provincial population of Rio Grande Do Sol indicated a 0.4 percent annual risk of infection, with a 2.4 fold higher risk in southern than in northern rural areas.

South-East Asia. Only Thailand had national survey data available, but repeated surveys of local area populations were available for both India and Indonesia. In these populations, annual risks in the decade of the 1970's appear to have ranged from about 1 to 5 percent. Annual risks were highest in Indonesia.

Based on the 1977-79 national survey, the annual risk of infection in Thailand was 2.2 percent in 1974. Two earlier surveys, one of Bangkok and Chiengmai Province in 1960-64, and one of localities of Chiengmai and Kanchanaburi Provinces in 1954, indicate annual risks only slightly higher than in the national survey 16 to 24 years later.

In India, three large local populations were twice surveyed. Declining trends of 1.6 and 3.5 percent a year were apparent in two of these populations, but an increase of about 1 percent was apparent in the third population. Village surveys in 7 regions throughout India in 1972 indicate annual risks on the order of 1 to 2 percent. The village survey in Kashmir, compared to a 1978 sample survey of the Kashmir Valley, suggest a declining annual trend, but the populations may be only nominally comparable.

Indonesia has followed a policy since 1974 of withholding BCG and conducting 5-yearly surveys in nine special areas selected to be situated throughout the country. Three surveys have been completed in five of these areas, two in three areas, and one in another area. There are also three surveys available from an area with low BCG coverage. The latest surveys in these areas indicate a median annual risk of 2.3 percent (range: 0.7 to 3.9). Earlier data from the 1964-65 survey in rural East Java indicate an annual risk of 1.6 percent. Comparing the earliest to the latest survey in each of the nine areas with repeated surveys, the median downward trend in the annual risk of infection was 2.5 percent a year (ranging from a decline of 6.3 percent to an apparent increase of 3.4 percent a year).

Eastern Mediterranean (and Algeria). For the purposes of this project, Algeria is grouped in this region instead of with the African countries. National survey data were available for six countries, and repeated surveys of local populations were available for a seventh country in this region. Recent annual risk levels appear to be low to very low in Bahrain, Libya, Algeria and Kuwait (0.2 to 0.5 percent), but high in Afghanistan and Pakistan (1.8 and 3.5 percent, respectively). Recent levels of risk in the Syrian cities of Aleppo and Homs also appear to be very low (0.3 and 0.14, respectively). The trend of risk also appears to have decreased steeply in the current low risk countries, but not as steeply in Pakistan and appears to have increased in Afghanistan.

Four local areas sampled in 1980-84 for the nearly completed national survey of Algeria had also been canvassed in the 1949-52 mass BCG campaign. Repeated surveys were also available for the population of Blida. Based on these comparisons, annual risk of infection appears to have decreased about 6 to 7 percent a year in Algeria. A similar trend is apparent between risk estimates for the Syrian cities of Aleppo and Homs.

In Kuwait between 1972 and 1981, all school entrants (including non-citizens) were tuberculin tested prior to BCG vaccination. Compared to the 1962-63 national sample survey estimate, the annual risk of infection appears to have declined by 10 percent a year. In Bahrain, a decline of nearly 12 percent a year appears to have occurred between the 1969 national sample survey and mass tuberculin testing of students in 1981. A similarly steep rate of decline may have occurred in Eastern Libya, if the areas and populations covered in the surveys are comparable.

The annual risk estimate based on the 1974-78 national sample survey of Pakistan, which was completed except for Baluchistan, compared to the estimate based on the mass BCG campaign of 1949-54, suggests that the risk of infection declined by 4.2 percent a year, but that the risk was still high (1.8 percent) in 1972. The risk estimate based on the partially completed 1961-62 national survey is consistent with this trend.

The annual risk of infection in Afghanistan appears high (3.5 percent in 1978), without having much changed since 1958, compared with an estimate based on tuberculin testing program data collected in 1963 in selected schools around the country.

Western Pacific. Eleven national sample surveys were available for five countries in this region. In the Republic of Korea, the annual risk of infection appears to be declining, but remains high at about 2 percent. The risk appears to be about 1.8 percent in the Philippines, based on the recent national survey. Infection risk appears to be relatively low in Malaysia (0.4 percent) and Samoa (0.5 percent).

In China the annual risk of infection appears to have been 1 percent in 1975, based on areas without BCG coverage in the very large 1979 national survey sample.

Based on infection risk estimates from the five 5-yearly national surveys available from the Republic of Korea, the trend appears to be downward at 3.8 percent a year to a level in 1984 of 2 percent.

IV. DISCUSSION

Interpretation of this collection of risk and risk trend estimates must take into consideration the many potential sources of error, both in determining absolute levels of risk and in comparing risk estimates among countries or between periods within the same country. Some of these sources of error appear to have been adequately controlled, but the influence of other sources of error (identified and unidentified) must be acknowledged as unknown.

Tuberculin skin testing is a usefully accurate technique for separating groups at relatively high and low risk of future Mycobacterium tuberculosis disease, but is liable to varying degrees of error in identifying all the infected and specifying all the uninfected.

Sensitization to environmental mycobacteria is a source of nonspecific reactivity to tuberculin that is especially prevalent in tropical regions (Edwards and Edwards, 1960). There was evidence in reaction size distributions of a high prevalence of nonspecific sensitivity in several of the African and Asian populations surveyed, but distribution data for older groups or for bacteriologically confirmed cases were frequently available for locating the mode of the distribution of true infections and deriving their number by assuming the distribution to be symmetric.

There is underlying variability in tuberculin reactivity as evidenced by the variation between simultaneously applied identical tests in the same individual (Chaparas et al, 1985). Although this reduces precision of estimation, it is not expected to introduce systematic error.

A variety of antigen preparations and dosages were used, and these differed between countries and within countries over time. Estimating the number infected by using the symmetry of the distribution of true reactions about the mode would adjust for differences in specific biological potency between antigen preparations, but would not be effective in controlling for large differences in specificity of antigens.

The Mantoux method of administration was virtually always used, and all the selected studies measured induration of reaction. Techniques of measurement varied somewhat, but almost always consisted of transverse measurement at 48 or 72 hours after administration.

Waning of tuberculin reaction size over time, and complete reversion to zero reactivity are recognized to occur (Sutherland, 1971). To the extent reversions have occurred in a population, tuberculin test prevalence at a point in time will underestimate the proportion who were ever infected. But limiting to groups of about the same low average age may have minimized and kept comparable the effects of cumulative reversion.

Boosting is a potential problem in survey designs that retest the same individuals (Styblo, 1984). Boosting is the effect of an initial tuberculin test which, although it elicits slight or no reactivity itself, apparently acts as an antigenic stimulus able to recall waned or reverted preexisting mycobacterial sensitivity so that a subsequent test does elicit reactivity that is indistinguishable from conversion caused by M. tuberculosis transmission in the interval between the tests. Although some of the data compiled in this project came from surveys using a repeated testing design, the problem of boosting was avoided by selecting age groups too young to have been tested in earlier rounds.

BCG vaccination, a major component of tuberculosis control activities in developing countries, compromises the usefulness of tuberculin testing as a means to survey risk of infection. Tuberculin skin testing cannot distinguish between sensitivity caused by BCG vaccination and sensitivity caused by natural infection with M. tuberculosis, because BCG vaccination, unlike nonspecific sensitization, causes reactions that are distributed with nearly the same mode and shape as reactions caused by true infections with M. tuberculosis. For this reason the risk of infection in the whole population can only be inferred from risk measured in the unvaccinated.

In some of the countries for which survey data were selected, the policy was to vaccinate indiscriminantly without using tuberculin testing to select the as yet uninfected. In these countries, surveys limited to children without evidence of vaccination are subject to bias only to the extent that children selected for vaccination, either by choice or by local availability, are at a different risk of infection than the unvaccinated. This is a potentially severe source of bias if BCG coverage is very high.

In some of the surveys selected for this project, none of those surveyed had been vaccinated, either because BCG had not been introduced into that locale, or because BCG was withheld by policy until a later age. In other surveys, the unvaccinated were identified by physical examination to detect the characteristic scar. Levels of coverage by BCG were very low in some surveys, in which case representation of the whole population by the unvaccinated would be unaffected. In a few surveys, BCG coverage was so high that representation was demonstrably affected.

In other countries, the policy was to tuberculin test and vaccinate only those with weak or no reactions. In this situation, a later survey among children without BCG scars would be liable to severe overestimation bias. This was avoided by selecting age groups before the age of eligibility for selective vaccination programs in effect in a particular country.

Failure to test and measure every person in a survey sample can introduce a bias if those not reached by the survey are at a different risk of infection than those who were reached. A severe bias might also result from failure to measure a high proportion of those tested, because whether a survey participant returned for reading could well depend on whether there had been a reaction. Surveys with severe problems of this kind were not selected. Adequate coverage was a criterion for selection by this project, and was high in most of the surveys selected.

Although the average annual risk for a group lies in the calendar interval from birth to the time of the survey, it need not be at the interval midpoint. If the risk is changing substantially over time, as data from several of the surveys indicate, or varies with age, as has been suggested by the work of Sutherland (1976), and as might be expected in some of the diverse cultures surveyed, a complex model is necessary to estimate the risk at a particular time (Styblo, 1969). Limiting to young, narrow age groups was used as a way to bracket risk estimates within usefully narrow time intervals.

Average annual risk estimates for the same populations surveyed in different years are connected with straight lines in Figure 2 to indicate the average trend that would result in the observed risk estimates. An exponential trend is to be expected in the situation of a long-term constant ratio of the number of new cases produced by each existing case (Sutherland, 1976). However, without data for intermediate years, it is difficult to know the true shape of a trend line. In some instances where more than 2 surveys were available, the trend appeared to follow a fairly constant geometric decrease, but in other instances, the trend appeared to have changed over time.

Many survey reports presented more detailed analyses of infection risk and its trend, but for the purposes of this review, methods were adopted that could be simply and consistently applied to all data. In the few instances of large disagreement, the present analysis may be in error.

V. CONCLUSIONS

This attempt to review and compile data available from major surveys carried out in developing countries since 1975 falls far short of providing a comprehensive picture of tuberculous infection risk and trend in the entire developing world. The assembled data cannot safely be generalized beyond the specific target populations surveyed. However, the assembled data do provide several recent objective examples of apparent progress and lack of progress in tipping the balance against the tuberculosis epidemic.

The review found that since 1975 many large scale surveys have been successfully carried out in the developing countries, with impressive attention to correct procedure and technique.

In most of the countries repeatedly surveyed in whole or in part, risk of infection does appear to have diminished. In some of these countries, the decline appears to have been substantial, and current levels of risk have become very low in a few countries.

In other countries, however, rates of infection appear to remain high and there is no indication of decrease.

It may be speculated that general improvements in living standards and tuberculosis control programs are having an effect against the tuberculosis epidemic in some parts of the developing world as it already has in the more developed countries. In the rest of the developing world, however, very little is known of the current magnitude and trend of the risk of tuberculous infection.

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TABLE 1. **ANNUAL RISK OF TUBERCULOSIS INFECTION IN DEVELOPING COUNTRIES BASED ON TUBERCULIN SURVEYS**[a]

I. WHO African Region (except Algeria)
II. WHO Region of the Americas
III. WHO South-East Asia Region
IV. WHO Eastern Mediterranean Region (and Algeria)
V. WHO Western Pacific Region

[a] See our web site at URL: www.who.int/bulletin