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From Exposure to Disease: The Role of Environmental Factors in Susceptibility to and Development of Tuberculosis

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INTRODUCTION

Throughout the first three quarters of the 20th century, the incidence of tuberculosis declined in industrialized countries (1, 2) (figure 1). Part of this decline may have been due to isolation of infectious tuberculosis patients in sanitariums and the pasteurization of milk, but it is generally thought that improved housing and habitat, decreased crowding, better hygiene and sanitation, use of clean water, and better nutrition all contributed to decreased tuberculosis notification (3–5). Since the mid-1980s, however, this decreasing trend has slowed down and has even reversed in some countries, such as the United States and the United Kingdom, calling for rapid epidemiologic investigations (6, 7). In the United States, the resurgence of the disease in the 1980s was attributed to a group of factors, including the epidemic of human immunodeficiency virus (HIV) infection, diminished public health efforts to control tuberculosis, rising poverty, homelessness, overcrowded conditions, and immigration from countries with a high prevalence of tuberculosis (8, 9). Identification of these high-risk groups and behaviors has stimulated actions to improve tuberculosis control activities, resulting in a reversed trend in tuberculosis notification rates after 1994 (10, 11). However, developing countries never experienced such a substantial drop, and the number of reported tuberculosis cases increased dramatically during the 1980s, especially in Africa south of the Sahara, where tuberculosis is a leading cause of mortality (12). From 1985 to 1991, the annual number of reported new cases tripled in Zambia, doubled in Malawi, and increased by 76 percent in Tanzania (13) (figure 2). This increase in tuberculosis case rates in developing countries has been attributed mainly to the combined effects of HIV infection, population growth, and poorly organized tuberculosis control programs with low case finding and cure rates (13, 14).

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Abbreviations: AIDS, acquired immunodeficiency syndrome; BCG, Bacillus Calmette-Guérin; DOTS, Directly Observed Therapy, Short-course; HIV, human immunodeficiency virus; SES, socioeconomic status.

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Socioeconomic factors have long been associated with tuberculosis (1–3), and recent US data show that they still play a role, in conjunction with the HIV epidemic (6, 9). In parallel, recent advances in the field of molecular biology and genetics have provided some evidence of the role of genetics in susceptibility to tuberculosis at the individual level, introducing a new dimension to understanding the immunologic correlates of protection against tuberculosis (15). Most of what we know about the natural history of tuberculosis and the effect of environmental factors on the disease comes mainly from studies conducted in developed countries over the last 60 years. With the recent work in the area of genetics, there is a need to reassess past studies on environmental factors in light of current knowledge. This paper reviews evidence of the contribution of environmental factors to the spread of tuberculosis infection and disease in populations. The first part summarizes existing evidence of the role of environmental factors in the risk of tuberculosis, separating the effects on the risk of infection and on the risk of disease and examining the aspects in developed and developing countries. The second part assesses the role of these factors in tuberculosis infection and disease, taking into account recent advances in the field of tuberculosis genetics.

Relevant studies were identified by searching the MEDLINE database (National Library of Medicine, Bethesda, Maryland) for articles published in English since the 1960s. The following keywords were used: tuberculosis, environment, contact, crowding, socioeconomic status, poverty, ethnic groups, migration, epidemiology, genetics. Additional and earlier studies were found in references cited in articles identified from the MEDLINE search and from textbooks. Particular attention was given to selecting papers reporting a measure of association between tuberculosis infection and/or disease and a specific factor or group of environmental factors.

NATURAL HISTORY OF TUBERCULOSIS DISEASE

Development of tuberculosis is a two-stage process in which a susceptible person exposed to an infectious tuberculosis case first becomes infected and may later develop the disease, depending on various factors. The endpoint of the chain (tuberculosis disease) depends on the succession of various factors influencing 1) the risk of exposure (meeting the "bug"), 2) the risk of infection in a second place (indicated by a positive tuberculin skin test), and 3) the risk

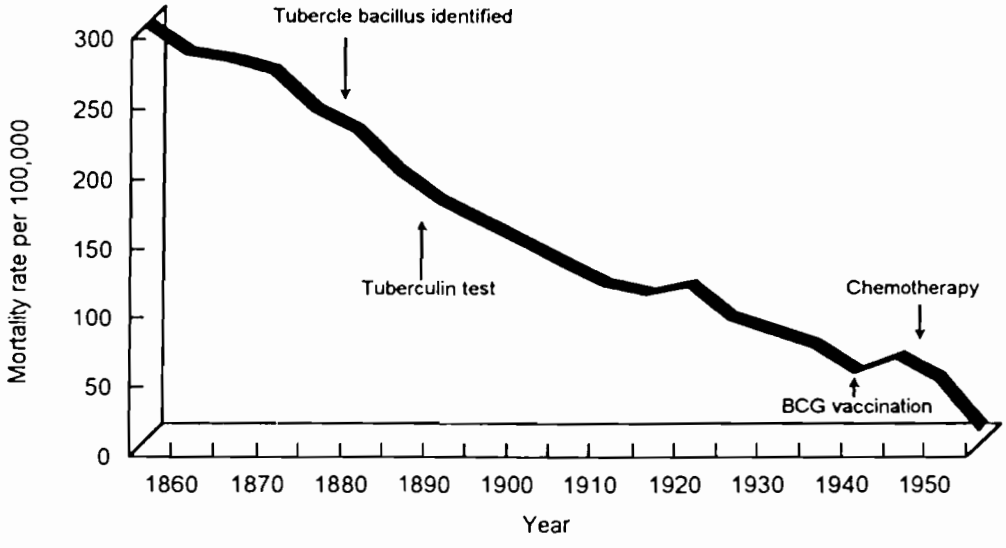

FIGURE 1. Annual tuberculosis mortality rates in England and Wales, 1850–1960. BCG, Bacillus Calmette-Guérin. (Adapted from the following source: Kass EH. Infectious diseases and social change. *J Infect Dis* 1971;123:110–14).

of developing disease. The particularity of tuberculosis is that, in persons exposed to the tuberculosis bacilli, acquisition of infection is often removed from development of disease and involves different physiologic mechanisms. Therefore, the risk factors for *infection* are quite different from those for *development of disease* after infection (16) (figure 3).

Risk of exposure

The first step is to meet the bug, that is, to come in contact with an infectious tuberculosis case who expectorates bacilli in the surrounding airspace. The likelihood of contact between a susceptible person and an infectious tuberculosis case depends on the prevalence of active pulmonary tuber-

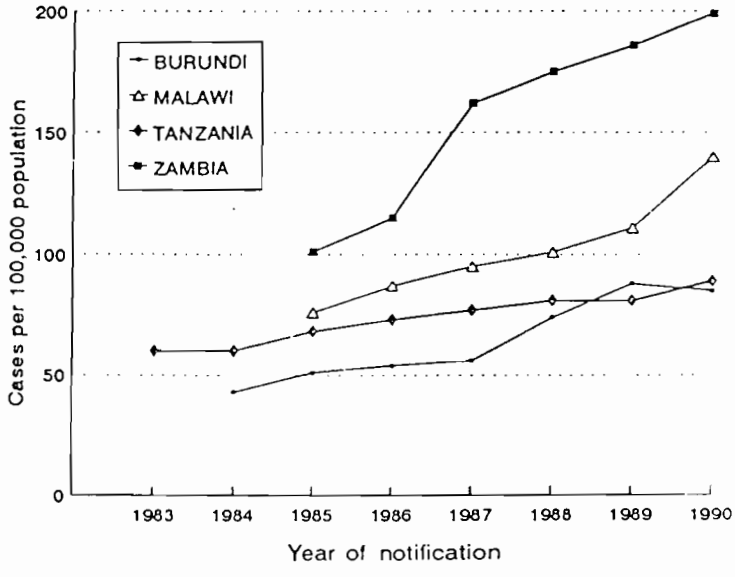

FIGURE 2. Notification rates of tuberculosis (all forms) in selected African countries, 1983–1990. (Adapted from the following source: Narain JP, Raviglione MC, Kochi A. HIV associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tuberc Lung Dis* 1992;73:311–21).

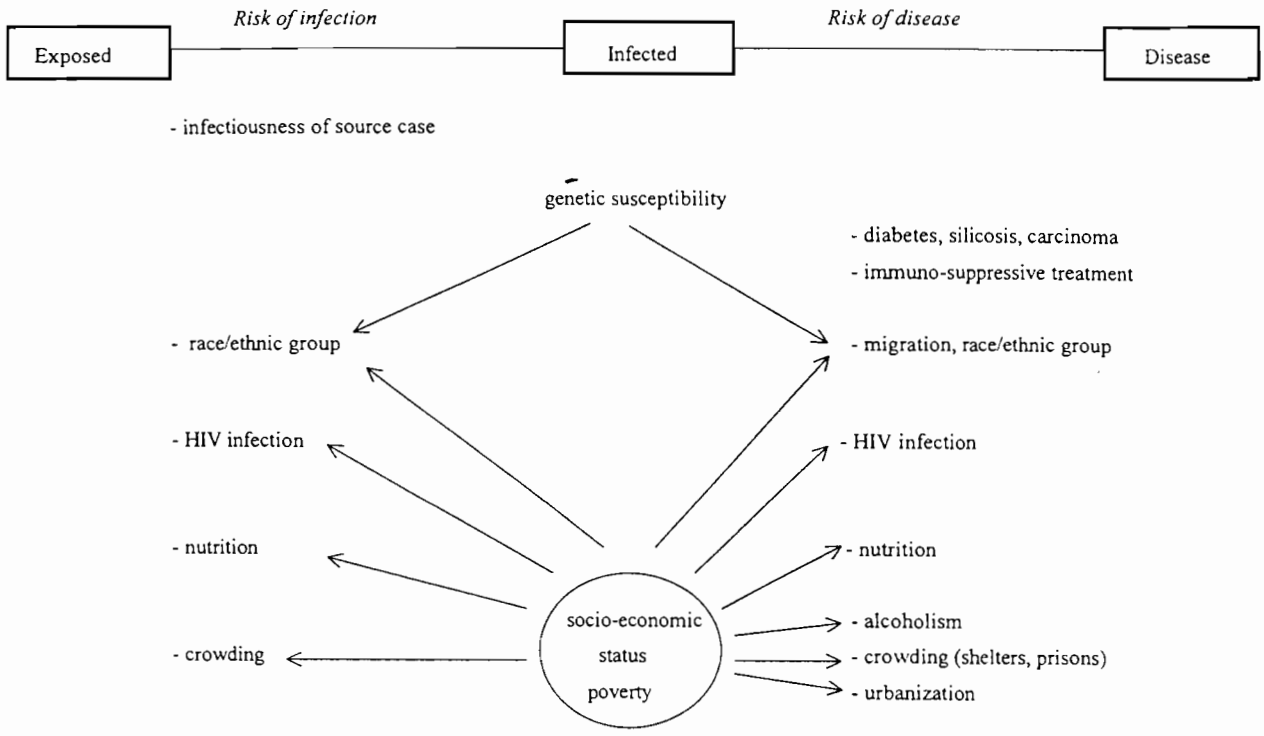

FIGURE 3. Impact of environmental factors on the risk of infection and development of disease after infection and their link with host-related factors. HIV, human immunodeficiency virus.

culosis in a given population and is influenced by several factors, the most important being crowding.

Risk of infection

Among persons exposed to an infectious tuberculosis case, the risk of becoming infected is determined primarily by the combined action of three factors: 1) the infectivity of the source case, 2) the degree of exposure of the susceptible person to that case, and 3) the degree of susceptibility of that person to infection. The infectivity of the case is a function of the frequency of coughing, the density of bacilli in the sputum (17, 18), and the microbial "virulence" (19–21). Several studies have shown that sputum-smear-positive pulmonary tuberculosis cases are more likely than sputum-smear-negative tuberculosis cases to infect their contacts (17, 22). The degree of exposure is determined by the proximity of contact between a susceptible person and the infectious tuberculosis case. Household studies conducted more than 30 or 40 years ago both in industrialized and nonindustrialized countries showed that the risk of becoming infected increased with intimacy of contact with a tuberculosis case (23–25). Data from nosocomial outbreaks of tuberculosis in HIV-infected subjects suggest that susceptibility to infection is dependent on the health status of the person (26, 27), and recent studies suggest that susceptibility to mycobacterial infection might be genetically modulated (28, 29).

At the population level, the risk of being infected is classically estimated by the annual risk of tuberculosis infection, which measures, in a given population, the proportion of persons who are primarily infected or reinfected with tubercle bacilli over one year (30). This measure is derived from the results of tuberculin surveys by converting information on prevalence of infection into a smooth series of annual rates of tuberculosis infection (31), and it is usually reported to be approximately 1–2 percent in developing countries and 0.1–1 percent in developed countries (32). It is generally estimated that about 10 persons are infected, on average, with tubercle bacilli during one year by one smear-positive case of pulmonary tuberculosis, but this number depends on the prevalence of sources of infection in the population (33).

Risk of development of disease

In patients infected with *Mycobacterium tuberculosis*, tuberculosis can develop at a variable time through reactivation of a previously acquired (latent) infection or exogenous reinfection (5, 33). The relative contribution of reactivation and reinfection is likely to depend on the epidemiologic context (34). It is generally accepted that in populations at high risk of infection, reinfection might be a major contributor to the overall rate of tuberculosis in adults, whereas, in populations that have a low risk of infection, most cases of postprimary disease in adults probably result from reactivation (33,

35). The time from infection to disease ranges from a few weeks to a lifetime (36). The risk of developing disease after infection has been reported to be much higher in the 5 years following infection and to decline as the time interval since infection increases (33). Once a person is infected, the cumulative lifetime risk of developing disease classically has been estimated to be approximately 10 percent (37), but a recent modeling study in which data from England and Wales were used showed that the lifetime risk of developing tuberculosis is strongly age and time dependent (38). In persons infected with *M. tuberculosis*, any condition modifying the balance established in the body between the tubercle bacilli and the host's immune defenses can affect risk of developing the disease. Factors that have been shown to influence this balance include HIV infection, immunosuppressive treatment, diabetes, malnutrition, and alcoholism, and all are considered *intrinsic* to the susceptible host (4, 16).

Any factor influencing the risk of infection and/or the risk of breakdown after infection affects the incidence of tuberculosis disease in a given population. While most factors that affect the risk of infection (such as crowding, urban residence, and low socioeconomic status (SES)) are *extrinsic* to the susceptible host and are related to the environment (39), many that affect the risk of disease after infection are a *consequence* of human interaction with the environment (figure 3). Environmental factors may have an impact on the incidence of tuberculosis in a given population as a result of their effect on both the risk of infection and the risk of disease once a person is infected. These factors are discussed in the following section, which separates their impact on the risk of infection or the risk of developing disease after infection (tables 1 and 2).

EFFECT OF ENVIRONMENTAL FACTORS

Crowding

More than 60 years ago, Frost observed higher attack rates of tuberculosis among persons in familial contact with pulmonary tuberculosis cases (40). Later, Chapman and Dyerly found an association between the risk of tuberculin conversion in children living in the house of an infectious tuberculosis case and the number of cubic feet per person in the house (41). This finding suggests that in crowded houses, a greater degree of shared airspace increases exposure to *M. tuberculosis*, which can even be increased by limited air movement in closed spaces—hence a greater *risk of infection*. Crowding also has been reported to increase the *risk of tuberculosis disease*. In a study investigating the influence of the "social complex" on tuberculosis notification and mortality in Glasgow, Scotland, between 1930 and 1947, Stein found a highly significant association of tuberculosis disease with various social variables, the strongest being crowding (average number of persons per house) (42). Later, this author found that tuberculosis mortality between 1950 and 1952 in Glasgow was highly correlated with crowding and that the number of new tuberculosis cases was highly correlated with *over*crowding (defined as the proportion of houses with more than two persons per room) (43). Similar results were found in a more recent study in the Bronx, New York, where children less than age 5 years living in severely crowded areas were about five times more likely to develop tuberculosis (adjusted for HIV status) than children living in areas with limited or no crowding (44). From 1982 to 1991, tuberculosis notification rates in London boroughs (United Kingdom) increased by 12 percent for each percentage increase in the number of persons living in overcrowded accommodations (45).

Although the association of tuberculosis with crowding has been clearly demonstrated in a number of studies in industrialized countries, only a few studies have investigated this association in resource-poor countries. Tuberculin surveys conducted in sub-Saharan Africa and in India by the World Health Organization in the late 1950s showed that tuberculosis infection usually was distributed evenly within households in given communities and that children living in the same household as an infectious tuberculosis case had a higher prevalence of infection than children living in other households, but the effect of crowding itself was not examined (24, 25). In a study in South Africa in 1986, no positive association was found between crowding and tuberculosis, but this finding may have been due to overmatching of cases and controls (46). However, no distinction was made between tuberculosis infection and disease, and there was no information on former vaccination with Bacillus Calmette-Guérin (BCG) or former exposure to tuberculosis.

Crowding increases the risk of exposure by increasing the likelihood of contact between susceptible persons and infectious tuberculosis cases as well as the intimacy of exposure. Persons exposed to an infectious tuberculosis case in a limited or closed environment thus may experience an increased risk of infection as compared with persons living in noncrowded quarters, and progression to disease might be enhanced by other factors modifying the host's immune defenses (such as malnutrition, depressed immune status, or HIV infection) (3–5). This particular situation has been well studied in prisons as well as in homeless shelters in the United Kingdom and the United States (47–49). In both situations, crowding increases the risk of exposure to an infectious tuberculosis case and therefore the risk of infection. In 1976, an investigation in a state prison in Arkansas found that tuberculosis morbidity was 6.5 times higher in the prison than in the general population (49). In New York City, the reported incidence of tuberculosis among prison inmates increased between 1976 and 1986 and was shown to be related to HIV infection and drug use (50). It was later found that development of clinical tuberculosis was significantly associated with time spent in prison (51). Similar findings have been reported in Malawi, where active tuberculosis case finding among 914 prisoners identified 47 (5.1 percent) tuberculosis cases, 16 (34 percent) of whom were infected with HIV (52).

The effect of exposure has been well studied in health care workers. Reports of outbreak investigations and surveillance studies have shown that health care workers are at increased risk of developing tuberculosis infection and disease (53, 54). While acquisition of *M. tuberculosis* infection was traditionally believed to require prolonged and intimate contact with an active pulmonary tuberculosis case, occupa-

TABLE 1. Environmental risk factors for tuberculosis infection

Risk factor	Type of study	Main findings*	Reference no.
Contact with source case	Contact studies	Proportion of tuberculin reactors among children in contact with the following: sputum-positive tuberculosis: 65.2%; culture-positive tuberculosis: 26.8%; culture-negative tuberculosis: 17.6% (general population: 22.1%).	17
		Severity of disease in index tuberculosis cases is the stronger predictor of infection among contacts ($r = 0.409$).	41
		Proportion of children (aged <15 years) infected in households of bacillary tuberculosis cases: 41%; households without tuberculosis cases: 12%.	25
		Higher proportion of tuberculin reactors among contacts of smear-positive cases than among contacts of smear-negative cases and than among the general population.	22
		Risk of infection among contacts increases with age, intimacy of contact, and infectivity of the source case.	22, 23
Crowding	Contact study	Tuberculin conversion in children living in houses of tuberculosis cases is associated with the number of cubic feet per person in the house.	41
	Tuberculin survey	Tuberculin reactors: 24.5/1,000 in houses with ≥1 person per room vs. 9.1/1,000 in houses with <1 person per room.	65
Urban residence	Tuberculin survey	Tuberculin reactors: 16.9/1,000 among urban residents vs. 12.6/1,000 among rural residents.	65
SES†	Tuberculin survey	Tuberculin reactors: 16/1,000 among students if head of household educated (>12th grade) vs. 69.9/1,000 if head of household not educated (<12th grade).	65
	Tuberculin survey	Tuberculin reactors: 22.4% among persons of low SES vs. 5.5% among persons of high SES.	67
Race/ethnic group	Tuberculin survey	Proportion of positive reactors: 8.4% in Whites, 26% in Blacks, and 30% in Puerto Ricans (age and SES adjusted).	67
	Tuberculin survey	Tuberculin reactors: 13.8% among Blacks vs. 7.2% among Whites (relative risk = 1.9, 95% confidence interval: 1.7, 2.1) in nursing homes.	116
	Outbreak investigation	Risk of tuberculin infection similar for Black and for White children in contact with a source case (relative risk = 0.98, 95% confidence interval: 0.78, 1.22).	118

* The measure of association is given as reported in the cited studies (coefficient of correlation, odds ratio, relative risk, proportions).
† SES, socioeconomic status.

tional studies have suggested that, under intensive exposure to airborne tuberculosis, limited contact with a single case of tuberculosis was sufficient for a person to become infected (53). This finding has been supported as well by recent studies of outbreaks of *M. tuberculosis* infection in close environments, such as airplanes (55).

Urbanization and homelessness

Urban centers have traditionally had higher rates of tuberculosis than rural areas (56). In the course of a clinical trial of BCG vaccination in Puerto Rico in 1949–1951, the rate of tuberculosis disease was 14 percent higher among urban than rural residents (37). In British Columbia (Canada), 1970–1985 notification rates were about two times higher in Vancouver than in the rural area of the province (57). Association between tuberculosis and urbanization is probably confounded by poverty and crowding, because residential crowding in low SES groups brings more persons (especially children) into contact with infectious cases of tuberculosis in people living in the same household (44).

In New York City, resurgent tuberculosis since the early 1980s has been attributed to high rates of tuberculosis in alcoholics, drug users, and homeless people (58); according to the authors of this study, the development of mass shelters for homeless populations exacerbated transmission of tuberculosis because persons whose tuberculosis was treated inadequately were gathered together in crowded shelters

TABLE 2. Environmental risk factors for tuberculosis disease

Risk factor	Type of study	Main findings*	Reference no.
Contact with source case	Contact studies	Risk of tuberculosis disease among contacts of smear-positive tuberculosis cases: 5.9%; contacts of smear-negative tuberculosis cases: 0.3% (general population: 0.015%).	22
Crowding	Ecologic study	Expected notification rate in households with an average of 0.9 person per room: 150/100,000; 1.6 person per room: 232/100,000.	42
	Ecologic study	From 1982 to 1991, the average notification rate increased by 12% for every 1% increase in the proportion of overcrowded households ($p = 0.002$).	45
	Ecologic study	The risk of tuberculosis is higher for children living in areas with more than 12% crowded dwellings compared with areas with fewer than 12% crowded dwellings: relative risk = 5.6, 95% confidence interval: 1.6, 19.8.	44
Urban residence	Routine data review	From 1970 to 1985, notification rates were two times higher in urban areas than in rural areas.	57
SES†	Routine data review	Annual notification rate from 1980 to 1982 in an urban population was as follows: for low SES: 242/100,000; for high SES: 2/100,000.	57
	Ecologic study	Notification rates of tuberculosis from 1985 to 1990 correlate with the Jarman ($r = 0.73$, $p < 0.0001$) and Townsend ($r = 0.59$, $p < 0.0005$) deprivation index.	68
	Case-control study	From 1988 to 1990, the risk of tuberculosis for persons of the lowest SES was fourfold the risk for persons of high SES (odds ratio = 3.7, 95% confidence interval: 1.5, 9.9).	70
	Ecologic study	From 1988 to 1992, there was a 35% increase in notification rates in the 10% poorest population with the highest crowding index.	69
Race/ethnic group	Ecologic study	US notification rates of tuberculosis, 1992: 4/100,000 for non-Hispanic Whites, 31.7/100,000 for non-Hispanic Blacks, 22.4/100,000 for Hispanics, 46.6/100,000 for Asians and 16.3/100,000 for Natives.	9
	Case-control study	There was a 7- to 20-fold increased risk of tuberculosis in non-Whites vs. Whites in Washington State.	70
Migration	National survey	In 1971, there was a 26% notification rate among the 2% foreign-born persons (India, Pakistan, Africa) in England and Wales.	106
	Ecologic study	The number of foreign-born cases accounted for 60% of the total increase in the number of tuberculosis cases from 1986 through 1992 in the United States.	9

* The measure of association is given as reported in the cited studies (coefficient of correlation, odds ratio, relative risk, proportions).
† SES, socioeconomic status.

with highly susceptible persons, including HIV-infected subjects. In a men's homeless shelter in New York City, tuberculous infection was found to be independently associated with increasing age, length of stay in the shelter system, and intravenous drug use (59). A study of a homeless shelter in Boston, Massachusetts, showed the importance of exogenous reinfection in explaining secondary tuberculosis among the homeless population (60). Later, a molecular epidemiology study conducted in Los Angeles, California, showed some evidence that tuberculosis among a homeless population was due to primary tuberculosis evolving from recent infection (61). Thus, the excess case rate of tuberculosis observed in poor urban districts is likely to be the result of a higher rate of current transmission of infection rather than a selective settlement of previously infected people in poor districts of the cities (57).

SES

Historically, tuberculosis has been linked with poverty (1, 62). Poverty conditions during the industrial revolution in the 19th century in Europe were accompanied by disease and death due to tuberculosis (2, 63). Disease rates in Europe declined constantly between the early 19th century (when approximately one death in four was caused by tuberculosis) and the mid-1980s (2, 64) (figure 1). Because this

decline started long before effective chemotherapy or vaccines were available, it has been attributed to the combined effects of isolation of infectious tuberculosis patients in sanitariums as well as socioeconomic development (2, 5, 64).

SES and infection. Several studies in North America and Europe have shown an association of SES and infection with *M. tuberculosis*. A study among high school students in Maryland in 1963 found that children from homes that ranked higher with respect to the educational level of the head of household, lack of crowding, and adequacy of housing had lower rates of tuberculin reaction (65). In a small sample of persons tested within a national health examination survey in the United States, tuberculin reactor rates were lowest among persons who had the most education, the highest incomes, the most skilled occupations, and the largest numbers of rooms in their homes (66). In a study of 52,000 school employees in New York City, tuberculin reactors were more frequent among persons of lower SES (22.4 percent) than among those of higher SES (5.5 percent), after adjustment for age, sex, and ethnic origin (67) (table 1).

SES and disease. The risk of disease in persons in Europe and North America has also been associated with SES. In Vancouver, the annual notification rate of active tuberculosis between 1980 and 1982 ranked from 242/100,000 persons in the sectors of the city with the lowest socioeconomic level to 2/100,000 persons in the sectors with the highest socioeconomic level (57). In Liverpool, 1985–1990 tuberculosis notification rates were strongly correlated with various measures of deprivation, independent of ethnic group (68). Between 1988 and 1992, the incidence of tuberculosis in England and Wales increased 35 percent in the poorest 10 percent of the population with the highest crowding index (69). In Washington State in the late 1980s, persons of the lowest SES were approximately four times more likely to develop tuberculosis than persons of the highest SES (70) (table 2).

The association of tuberculosis with socioeconomic factors has received little attention in developing countries. In an urban area in South Africa, no association was found between socioeconomic factors (general living conditions, ownership of luxury items, protein consumption, and education) and the individual risk of tuberculosis, but controls were not clearly selected and data analysis was inconclusive (71). In a recent study in rural Malawi, it was found that schooling and quality of housing were positively and independently associated with an increased risk of tuberculosis disease, after adjustment for baseline HIV status, age, and sex (72). The results from Malawi contrast with the findings from industrialized countries and may be explained by a differential access to health care services among various strata of society in rural areas in Africa.

Measurement of poverty. Almost all health indicators show an association between ill health and poor socioeconomic conditions (73–75). When the complex issue of assessing the impact of SES on tuberculosis is raised, the main difficulty is to determine the measure of deprivation, and different authors have used various indicators. The most frequently used indicators of deprivation reflect the SES of the persons or families, such as median household income, crowding, level of education, unemployment, public assistance, housing, and social class (65, 68, 69). Complex indicators, including several components, have also been used (68, 69), such as the Townsend overall deprivation index (68) and the Jarman index (69).

The large variety of indices used by different authors renders comparisons between studies difficult. All of these indicators reflect how the multiple components of the "poverty complex" are deeply interrelated and act together as risk factors for tuberculosis, although none intrinsically "causes" tuberculosis. For instance, the strong association observed in several studies between unemployment and risk of tuberculosis can probably be explained by the effect of various socioeconomic correlates (such as low income, crowding, poor access to health care, poor nutrition, and alcoholism) that are all related to unemployment. Thus, in Vancouver, unemployment was the single most important predictor of the notification rate of tuberculosis in the city for males aged 25–64 years, and the highest incidence of tuberculosis was found in the lowest income group that included the highest proportion of unemployed persons and alcoholics (57). In a population-based survey in the United States that collected occupational information on 9,534 patients with clinically active tuberculosis, the rate of tuberculosis among the unemployed group was 337.2/100,000 as compared with 4.9/100,000 among persons classified as "currently employed," after adjustment for age, sex, race, and foreign birth (76). Unemployment thus acts as a proxy for low SES.

Similarly, poverty results in overcrowded living conditions, which have been associated with a higher infection and disease rate. In the Bronx, New York, crowding was associated with a number of poverty-related variables, such as number of persons per family, number of children less than age 5 years, proportion of female-headed households, education, public assistance income, and absence of a telephone (44). By increasing the risk of exposure to infectious tuberculosis, overcrowding mediates much of the association between social deprivation and risk of tuberculosis. In addition, social deprivation reduces access to health care services. Therefore, most indicators of poverty work mainly as markers of crowding or poor access to health care. Lastly, poverty also may affect susceptibility to infection and development of disease through the indirect effect of poor nutrition or depressed immune status, as in the case of HIV infection (77, 78). Each variable of social deprivation used in various studies contributes in part to the impact of the "poverty complex" on tuberculosis. The existence of an SES-health gradient, in which tuberculosis risk increases at a relatively constant rate with decreasing SES, was recently shown in the United States and can be considered to summarize the effect of the different SES variables on tuberculosis (79).

Access to health care

Delays in diagnosis and treatment increase morbidity and mortality from tuberculosis as well as the risk of transmission of tuberculosis in the community (2, 80). Delays in diagnosis of tuberculosis have been reported in both devel-

oped and developing countries (81–84). The time period between onset of tuberculosis symptoms and diagnosis of tuberculosis is highly variable and depends on numerous factors, including the person's perception of disease, the severity of the disease, access to health services, and the expertise of health personnel (85, 86). In the United States, social deprivation was shown to reduce access to health care services, thus increasing tuberculosis morbidity and mortality (58). In Ghana and in The Gambia, the time period between onset of symptoms and initiation of therapy was shorter for patients living in urban areas than for those living in rural areas, showing the impact of differential access to health services (85, 87). In Zambia, the economic burden on patients due to lost income, transportation costs, and food expenditures was an important contributing factor to delayed diagnosis and hence continued disease transmission within the community (88).

Effect of age and sex

Age and sex variations in the prevalence of tuberculosis infection and disease have been reported worldwide, in both developed and developing countries (34, 89, 90). Early tuberculin skin test surveys have shown that infection with *M. tuberculosis* increases with age and then declines in older adults (24, 25). The prevalence of tuberculin sensitivity is usually similar in males and females until adolescence, after which prevalence is higher among males (89, 91). This difference after adolescence may reflect greater exposure among adult males because of differentiated social roles and economic activities (92), but it also may reflect a genuine sex difference in susceptibility to tuberculosis infection related to a different predisposition to responsiveness to delayed-type hypersensitivity (93).

In children less than 5 years of age, the risk of progressive tuberculosis disease after primary infection has been shown to be high, probably reflecting a high dose challenge within the home environment (contacts of smear-positive tuberculosis cases) (93). The risk then decreases until age 12 years and rises again in young adults, as has been shown in a controlled trial of BCG vaccination in Puerto Rico (37). Most tuberculosis in adults arises many years after primary infection because of exogenous reinfection or endogenous reactivation of a latent focus of infection (30). Age and sex differences in the distribution of tuberculosis disease have been reported in many countries (13, 90, 91). These differences can be explained by differences in case-detection and case-finding activities (92) or by true differences in susceptibility to disease (93). It is probable that, in addition to genuine age and sex differences in susceptibility related to biologic mechanisms, socioeconomic and cultural factors may play a role in determining age and sex differences in rates of infection, progression to disease, and treatment outcome (92).

HIV infection

HIV infection has emerged as the most important risk factor for development of tuberculosis in persons infected with *M. tuberculosis* (3, 5, 94). Because of the immunosuppression caused by HIV infection, persons with latent tuberculosis as well as newly infected persons may progress rapidly to clinical disease (78). The estimated risk of clinical disease in HIV-infected persons is between 6 and 26 times the risk in non-HIV-infected persons (95). By mid-1992, an estimated 5.6 millions persons were dually infected with HIV and *M. tuberculosis* worldwide, 3.8 million of them in sub-Saharan Africa (96). The number of new tuberculosis cases attributable to HIV infection was estimated to be approximately 300,000 in 1990 (4.2 percent of the total new tuberculosis cases) and was expected to rise to 1.4 million cases (14 percent) per year by the year 2000, 40 percent of them in sub-Saharan Africa (97). However, recent calculations based on 1997 data showed that the proportion of tuberculosis cases with HIV infection has not increased as fast as these forecasts and might be 8 percent (640,000 new tuberculosis cases) (98). The burden of HIV is exceedingly high in sub-Saharan Africa, although the number of tuberculosis cases co-infected with HIV varies greatly among African countries (98).

Structural and environmental factors have been found to make a significant contribution to the spread of HIV infection in developed and developing countries (99). The relation between economic underdevelopment, poverty, and acquired immunodeficiency syndrome (AIDS) is apparent cross-nationally (77). In return, AIDS exacerbates poverty in countries hit hard by the epidemic, contributing to a cycle of underdevelopment and AIDS-related mortality (100). At the community level, evidence exists that social class and ethnicity are associated with differences in HIV seroprevalence (101).

Urbanization has largely increased in many resource-poor countries over the past 30 years and has dramatically enhanced HIV transmission at multiple levels: by bringing people closer together in time and space and in environments with fewer social control mechanisms, urbanization has enabled HIV infection to spread in densely populated areas (102). Migration has been associated with the spread of HIV infection, especially in Africa (103, 104). For these reasons, factors that increase HIV infection will clearly contribute to increase the tuberculosis incidence related to HIV.

GENETICS AND THE ENVIRONMENT

Immigrants from countries with a high prevalence of tuberculosis have been reported to contribute to the increase in tuberculosis cases in the United States and the United Kingdom, and the risk of tuberculosis in ethnic minorities in the United States has been reported to be higher than in the general population (6, 8, 64). For some authors, the differences in tuberculosis risk among various ethnic groups are genetically determined, whereas, for others, this difference is related primarily to differences in socioeconomic conditions. This issue is debatable and has far-reaching consequences in terms of public health and tuberculosis control. To examine the terms of the debate, I will first review evidence of differences in the risk of tuberculosis among migrants and ethnic minorities in industrialized countries and then review data showing the effect of genetic factors on the risk of tuberculosis.

Migration

An early review of tuberculosis notification in Birmingham, United Kingdom, in 1958 showed that notification rates among migrants from Pakistan or India were four to six times higher than in the White English population, reflecting higher rates in the country of origin (105). In a national survey undertaken in England and Wales by the British Thoracic Association in 1971, 32 percent of tuberculosis notifications in the United Kingdom were among persons born outside the country, representing only 5 percent of the population (106). More important, in a similar survey in 1978, the rates of tuberculosis disease in children of Indian subcontinent origin born abroad (i.e., in a highly prevalent area) were 10 times higher than in White English children (living in a low-prevalence area). However, among children of Indian subcontinent origin born in the United Kingdom, these rates were three times higher than in White children, probably related to a higher risk of exposure at home and the presence of adverse socioeconomic factors (107).

In a 1966 tuberculin survey of Commonwealth migrant children in Bradford, England, tuberculin positivity rates were higher for immigrants than for children born in the United Kingdom, indicating higher rates of tuberculosis infection before arrival (108). A study among Scandinavian immigrants in Canada showed that, even after a long duration of residence in the country of adoption, tuberculosis rates were very similar to rates in the country of birth (109). These data suggest that, in a migrant group, early tuberculosis experience predetermines future susceptibility to tuberculosis disease throughout life. If migration occurs from an area of low incidence to an area of higher incidence of tuberculosis, then a number of people are likely to undergo primary infection in the new environment, so that tuberculosis develops within the first few years after entry (110). Conversely, groups of people moving from an area of high incidence of tuberculosis to an area of lower incidence include a number of tuberculosis cases whose disease will become manifest any time after migration. A DNA fingerprint analysis of tuberculosis patients detected between 1992 and 1994 in New York City found that 84 percent of the tuberculosis cases among foreign-born persons resulted from reactivation of infections acquired abroad (111).

In a 1991 study in London districts, ethnic origin was reported to be more important in explaining geographic variation in tuberculosis rates than the index of social deprivation (112). However, Mangtani et al. (45) and Bhatti et al. (69) found that the recent increase in tuberculosis case rates in England and Wales in the last decade was attributable mainly to socioeconomic factors (such as overcrowding and unemployment) rather than immigration. A recent review of tuberculosis notification rates in metropolitan areas of the United Kingdom in 1991 showed a significant association between the proportion of migrants and the measures of social deprivation (113). Similarly, in Massachusetts, it was recently found that the foreign-born population in the United States was considerably more resource-poor than its US counterparts (114). The higher incidence of tuberculosis in migrants as compared with the indigenous population thus could be explained by the combined effects of a higher risk of infection in the country of origin and differences in SES in the host country related to resettlement problems.

Effect of race/ethnicity on infection and disease

Infection. Studies in Georgia and Alabama in the 1950s found that tuberculin reaction rates were higher in Blacks than in Whites (16). In a study of the employees of the New York City board of education, race was the strongest risk factor for tuberculosis infection in each age group, after control for SES (67) (table 1). It has been suggested that the difference in the risk of *infection* observed among ethnic groups reflects genetic differences between human populations (115). In a study examining the rate of tuberculin conversion among 25,398 tuberculin-negative residents of 165 racially integrated nursing homes in Arkansas, Stead et al. found that Blacks were almost twice as likely as Whites to show evidence of a new infection (relative risk = 1.9, 95 percent confidence interval: 1.7, 2.1) (116). The prevalence of infection at entry into the nursing homes was twice higher in Blacks than in Whites, but there was no racial difference in the percentage of infected residents who developed clinical tuberculosis later in the absence of preventive chemotherapy. The authors concluded that a racial difference exists in susceptibility to infection with *M. tuberculosis* and that factors influencing susceptibility to infection are quite different from those controlling progression to clinical disease. However, when looking at racial differences in susceptibility to tuberculosis, Stead et al. did not examine potential differences in the prevalence of other risk factors between Blacks and Whites. While controlling for age, sex, and percentage of Black residents in nursing homes, these authors did not control for factors such as intercurrent disease, immunosuppressive treatment, nutritional status, or previous pulmonary disease, all known to increase susceptibility to tuberculosis. They also did not control for proximity of exposure to the infectious case, which has been shown to be a major factor for infection (22). Lastly, it is very likely that the higher percentage of tuberculin reactors among Blacks at entry into nursing homes reflects differential exposure in the community from which they originate rather than ethnic differences in susceptibility (117).

An outbreak of tuberculosis in a racially mixed elementary school in Missouri afforded the opportunity to reassess Stead et al.'s findings (116) in a controlled setting, taking into account degree of exposure to the infectious case (118). Of 343 students in this school who had contact with a physical education teacher suffering from cavitary pulmonary tuberculosis, 176 (51 percent) were found to be tuberculin-skin-test positive. Among these, Black children were no more likely than White children to be infected (relative risk = 0.98, 95 percent confidence interval: 0.78, 1.22), after adjustment for age, sex, and degree of exposure to the infectious case. Unfortunately, baseline tuberculin skin test results in this population were not known, but the authors found that Black children who were skin-test positive after exposure to the infectious case were more likely than White children to have larger skin-test reactions and to have abnormal chest radiographs.

Disease. Excess rates of tuberculosis *disease* have long been observed among racial/ethnic minorities in the United States (119, 120). In 1992, the annual, per-100,000 incidence of tuberculosis was 4.0 in Whites, 16.3 in Native Americans, 22.4 in Hispanics, 31.7 in Blacks, and 46.6 in Asians (9). From 1988 to 1990 in Washington State, a 7- to 20-fold increase in the risk of tuberculosis was observed in non-Whites compared with Whites and was reported to be due to higher exposure to *M. tuberculosis* in non-Whites and to higher progression to disease associated with low SES and HIV infection (70). However, in the course of a BCG vaccine trial in Puerto Rico, no major difference was found in the incidence of tuberculosis between Black tuberculin reactors and White tuberculin reactors (37). Therefore, considerable evidence exists that differences in tuberculosis transmission and morbidity between racial/ethnic groups result primarily from differences in exposure to tuberculosis and prevalence of tuberculosis infection due to differences in SES and crowding among racial and ethnic groups in the United States (6, 70). To quantify the proportion of increased risk of tuberculosis among racial and ethnic minorities attributable to SES, Cantwell et al. combined information on tuberculosis incidence in the United States from 1988 to 1993 with US census data (79). They found that approximately half of the increased risk of tuberculosis previously ascribed to race/ethnicity among US-born Blacks, Hispanics, and Native Americans could be explained by differences in SES. They also suggested that many social components of the racial and ethnic categories, other than genetically determined susceptibility to tuberculosis infection, probably explain the residual difference.

Implication of genetic factors

Various lines of evidence indicate that genetic factors determine in part differences in host susceptibility to infection with mycobacteria and that they might contribute to the pattern of clinical disease. The most convincing evidence comes from twin studies: because twins theoretically share the same environment, higher concordance rates for monozygous than for dizygous twins suggest that genetic factors are important in susceptibility to tuberculosis (121, 122). Genetic studies have shown a possible association of the *HLA-DR2* allele with susceptibility to tuberculosis (123). In mice, a gene coding for resistance to BCG has been identified (*Nramp*), which also controls resistance to leishmaniasis and *Salmonella* infection (124, 125).

Several polymorphisms have been described within the human homologue gene, *NRAMP1*, and it has been suggested that they could influence its function (126). A case-control study in The Gambia showed that *NRAMP1* gene polymorphisms were significantly associated with tuberculosis susceptibility, although it was not possible to distinguish between susceptibility to infection with *M tuberculosis* and susceptibility to disease progression (127). A mutation in the interferon-γ (IFN-γ) receptor has been identified as the cause of disseminated mycobacterial disease in a Maltese kindred (28), and a survey of cases of disseminated BCG infection following immunization in France revealed that a quarter of all cases were offspring of consanguineous parents (128). Mutations in the interleukin-12 receptor genes have been found to be associated with impaired immune defense against mycobacteria in humans (29, 129). A recent case-control study among Gujarati Asians in London suggested that polymorphism in the vitamin D receptor gene, combined with 25hydrocholecalciferol deficiency, could contribute to susceptibility to tuberculosis, although subsequent correspondence showed that data were inconclusive (130). Lastly, a genome-wide search of affected sibling-pair families from The Gambia and South Africa identified potential susceptibility loci on chromosomes 15q and Xq (131). Genetic factors thus might play a role in susceptibility to tuberculosis, although their level of action, as well as the specific physiologic pathways, remain to be fully understood, as does their relative importance given the large role that environmental factors play in the incidence of tuberculosis.

CONCLUSION

Tuberculosis is a multifactorial disorder in which environment interacts with host-related factors, contributing to the overall phenotype. Many factors play a role in individual susceptibility to *M. tuberculosis*. Understanding the individual balance between degree of exposure and inherited genetic susceptibility to infection, as well as the respective effects of environmental and host-related factors in development of tuberculosis disease, will have strong implications on tuberculosis control and prevention. However, there are several difficulties in trying to evaluate the role of these factors in the risk of tuberculosis, which are described in the paragraphs that follow.

The risk of infection and the risk of disease: A large number of studies examining the effect of environmental factors on tuberculosis did not differentiate between infection and disease, thus confusing the effect of these factors on the risk of becoming infected and on the risk of developing disease after infection. Rigorous studies are needed, separating clearly the effects of specific factors on the risk of *infection* and on the risk of *developing disease after infection*. Data are needed on the rates of disease by place and person according to the various risk factors, adjusted for rates of tuberculin reactivity and/or history of BCG vaccination.

The clinical presentation of tuberculosis: The majority of studies reviewed here were based on identification of smear-positive pulmonary tuberculosis. Tuberculosis can manifest clinically in various forms, usually separated into smear-positive, smear-negative pulmonary disease and extrapulmonary disease. Because geographic and ethnic variations in the distribution of the clinical forms of tuberculosis have been observed (64), it is probable that risk factors for smear-positive and smear-negative tuberculosis might differ, as has been shown with HIV infection, which tends to increase the risk of smear-negative or extrapulmonary tuberculosis (132). As suggested for leprosy, genetic factors might be involved in the development of specific clinical types of tuberculosis (133).

The components of the "poverty complex": Variation in the reported association between tuberculosis risk and various components of the poverty complex may be related to

the lack of power of some of the studies to detect an independent association with any of these components (employment, social class, or other factors). In the study by Bhatti et al., the high correlation observed between crowding and ethnic minorities and between crowding and the Jarman index makes it difficult to attribute the increase in tuberculosis notification rates to specific independent factors and to show the strong interrelation of all of these components (69). It is thus difficult to separate the effect of the various components of the poverty complex on tuberculosis and, when assessing the effect of a particular factor, to avoid confounding and interaction, even when multivariate models are used. This difficulty has been well described in the study by Cantwell et al., who demonstrated the existence of an SES gradient in relation to the risk of tuberculosis in the United States (79). Socioeconomic factors work at both the individual and community levels, and epidemiologic studies conducted to determine the effect of specific elements of the poverty complex on the risk of tuberculosis, after adjustment for specific confounding factors, suffer methodological limitations. Thus, ecologic studies may overestimate the strength of the exposure/disease association or assign erroneously group-based measures of disease-exposure association to persons within the group (ecologic fallacy) (79, 134).

The North/South divide (135): There are major differences in the distribution of tuberculosis infection (as measured by tuberculin surveys) and disease (as measured by case-notification rates) in industrialized and nonindustrialized countries (12, 33). However, research on environmental factors affecting the incidence of tuberculosis infection/disease over the last 50 years has been conducted mainly in industrialized countries, and few studies have tried to assess the role of these factors in the transmission of tuberculosis in resource-poor countries. In industrialized countries, the increased notification of tuberculosis cases has led to the investigation of individual risk factors in order to identify high-risk groups on which to target tuberculosis control activities (6, 8). This attitude has been implemented in some places (such as New York City) where tuberculosis control activities have been greatly expanded, with improvement in laboratory support and generalized use of Directly Observed Therapy resulting in a rapid decline in tuberculosis notification (10). In resource-poor countries, however, on the basis of high levels of prevalence of infection measured in tuberculin surveys in the 1960s, the prevailing attitude has been to consider the general populations of these countries as being primarily at risk (89, 90).

Dramatic reports of increased tuberculosis notification rates in resource-poor countries have reinforced this view (12, 13), and the priority has been not to identify high-risk groups but to cut the chain of transmission in the community by increasing detection of infectious tuberculosis cases and ensuring high rates of treatment completion (14). Subsequently, because case detection remains largely passive, most world public health efforts to fight tuberculosis remained focused on treatment. In 1991, the World Health Organization set up the objectives of treating successfully 85 percent of the tuberculosis cases and of detecting at least 70 percent of the smear-positive tuberculosis cases by introducing DOT,S (Directly Observed Therapy, Short-course) (136). However, DOT,S implementation has been slower than anticipated; in 1995, the DOT,S strategy was estimated to be accessible to only 23 percent of the world population (137). In view of the continuous rise in the incidence of tuberculosis in nonindustrialized countries, the question arises whether delivery of DOT,S is the only possible intervention for efficient tuberculosis control. By knowing the effects of several environment-related factors on tuberculosis, should the current approach to tuberculosis control remain predominantly treatment based, without matching efforts on prevention (62, 135)?

Several approaches can be considered to target tuberculosis control activities. The epidemiologic approach aims to identify risk factors for infection/disease (either genetic, biologic, or environmental) to reduce the risk of disease at the individual level. The sociologic approach tries to understand the complex relation between socioeconomic forces and tuberculosis infection/disease to reduce the risk of transmission at the population level (138). Innovative strategies for tuberculosis prevention and control must be developed. While new areas are being explored to develop new vaccines or to improve BCG vaccination to ensure proper and efficient protection (139), there is an urgent need to design new interventions against tuberculosis, integrating the epidemiologic and sociologic approaches (140). Comparison of the prevalence of individual risk factors for tuberculosis in various populations using standardized indicators would elicit useful information about the dynamics of tuberculosis transmission. The sociologic approach in which qualitative studies are used would help in understanding the complex relation between socioeconomic forces and tuberculosis transmission in both developed and developing countries (141). Better understanding of how socioeconomic background is associated with specific risk situations would help in designing new interventions aimed at modifying the environment to minimize the risk of disease at both the individual and population levels (142). It is doubtful that knowledge of genetic variation in the risk of tuberculosis will have any major public health impact, because targeting persons at increased risk of tuberculosis would be rather ineffective. However, it is hoped that this knowledge will lead to a greater understanding of the immunologic pathways at work in tuberculosis and offer new insights into tuberculosis treatment and prophylaxis (15). It has been suggested that investigation of gene-environment interactions will make it possible to determine the association between risk factors and disease more accurately, to clarify causal pathways, and to contribute to disease prevention (143). While we wait for new vaccines to be developed and tried, the respective roles of environment and genetic factors must be investigated further to improve tuberculosis control through better prevention and care adapted to various situations (144).

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