Investigation of Environmental and Host-related Risk Factors for Tuberculosis in Africa. I. Methodological Aspects of a Combined Design

C. Lienhardt, S. Bennett, G. Del Prete, O. Bah-Sow, M. Newport, P. Gustafson, K. Manneh, V. Gomes, A. Hill, and K. McAdam

Host-related and environmental factors for tuberculosis have usually been investigated separately using different study designs. Joint investigation of the genetic, immunologic, and environmental factors at play in susceptibility to tuberculosis represents an innovative goal for obtaining a better understanding of the pathogenesis of the disease. In this paper, the authors describe methods being used to investigate these points in a West African study combining several designs. Patients with newly diagnosed smear-positive cases of tuberculosis are recruited. The effect of host-related factors is assessed by comparing each case with a healthy control from the case's household. The role of environmental factors is estimated by comparing cases with randomly selected community controls. The frequencies of candidate gene variants are compared between cases and community controls, and results are validated through family-based association studies. Members of the households of cases and community controls are being followed prospectively to determine the incidence of "secondary" tuberculosis and to evaluate the influence of geographic and genetic proximity to the index case. This type of design raises important methodological issues that may be useful to consider in studies investigating the natural history of infectious diseases and in attempts to disentangle the effects of environmental and genetic factors in response to infection. Am J Epidemiol 2002;155:1066–73.

epidemiologic methods; genetics; infection; Mycobacterium tuberculosis; research design; risk factors; tuberculosis

The development of tuberculosis in humans is a two-stage process in which a susceptible person exposed to an infectious case first becomes infected and second, after an interval of years or decades, may later develop the disease, depending on a variety of factors. Since the acquisition of infection is often far removed from the development of disease and involves different physiologic mechanisms, the risk factors for infection are quite different from the risk factors for development of disease following infection (1). This has important implications for tuberculosis prevention and control (2).

Among persons exposed to someone with an infectious case of tuberculosis, the risk of becoming infected is determined primarily by the combined action of three factors: 1) the infectivity of the source case (which is itself a function of microbial virulence and the density of bacilli in the spum), 2) the intensity of the susceptible person’s exposure to the case, and 3) the susceptibility of the exposed person to infection (3–5). Factors reported to influence the risk of mycobacterial infection include age, sex, crowding, socioeconomic conditions, urbanization, racial/ethnic group, and human immunodeficiency virus infection (6, 7). In patients infected with Mycobacterium tuberculosis, the disease can develop at any time through reactivation of a previously acquired (latent) infection or through exogenous reinfection (8, 9).

The time interval from infection to disease ranges from a few weeks to a lifetime (9). The risk of developing disease after infection is strongly age and time dependent (10) and has been reported to be much greater in the 5 years following infection and to decline as the time interval increases (11). In a study of young children who were strongly posi-
tive reactors, the lifetime risk was reported to be as high as 10 percent (12). Any condition modifying the balance established in the body between the tubercle bacilli and the host’s immune defenses can have an impact on the risk of developing the disease. Factors that have been shown to influence this balance include age, sex, human immunodeficiency virus infection, immunosuppressive treatment, diabetes mellitus, malnutrition, alcoholism, and Bacillus Calmette-Guérin vaccination (1, 6, 9). Any factor influencing the risk of infection and/or the risk of breakdown after infection has an effect on the incidence of tuberculosis (7).

Clustering of tuberculosis within families has been recognized for a long time, but it is not clear whether this reflects genetic factors predisposing people to infection and/or disease, shared environmental factors, or the facility of transmission of infection within the home (13, 14). Epidemiologic studies have demonstrated that risk of tuberculosis is increased among close contacts of sputum smear-positive patients and that the prevalence of active disease increases with the intimacy of contact (15–17). High rates of transmission were found within households of smear-positive tuberculosis patients living in areas of high prevalence (18). However, it has been suggested that the majority of cases in the community are acquired from an unknown nonintimate contact (19). Molecular epidemiologic studies have found patients with no obvious epidemiologic relation to each other to be infected with the same strain of M. tuberculosis, which suggests that tubercle bacilli can be transmitted during brief contacts between persons who do not live or work together (20, 21). Thus, it remains unclear whether most transmission of tuberculosis takes place within households or outside of households (9).

Various lines of evidence indicate that genetic factors partly determine differences in host susceptibility to mycobacterial infection and that such factors might contribute to the pattern of clinical disease (14). Studies in twins have found higher concordance rates for monozygous twins than for dizygous twins, which suggests that genetic factors are important in susceptibility to tuberculosis (22, 23). A number of genetic studies have demonstrated an association between human leukocyte antigen haplotypes and susceptibility to the disease (24). A case-control study carried out in The Gambia showed that polymorphisms in the NRAMP1 gene were significantly associated with susceptibility to tuberculosis, although it was not possible to distinguish between susceptibility to acquisition of M. tuberculosis infection and susceptibility to disease progression (25). Recent case-control studies conducted among Gambians (26) and among Gujarati Asians in London, United Kingdom (27), found that a polymorphism in the VDR gene is associated with susceptibility to tuberculosis. Lastly, a genome-wide scan of sibling pairs from The Gambia and South Africa identified potential susceptibility loci on chromosomes 15q and Xq (28). Thus, genetic factors appear to play a significant role in susceptibility to tuberculosis, although their level of action and the physiologic pathways involved remain to be fully understood.

Experimental evidence indicates that interferon-γ, a cytokine produced by type 1 helper (Th1) lymphocytes, plays a central role in immune defense against tuberculosis (29). Mutations in the interferon-γ gene or the interleukin-12 receptor gene have been identified among children with disseminated nontuberculous mycobacterial disease (30–32). The fine balance between the production of Th1 and type 2 helper (Th2) cytokines appears to be important for the determination of host resistance or susceptibility to mycobacterial infection. Disruption of this balance in favor of Th2 cells could affect the ability of the host to express a protective immune response against M. tuberculosis and has been proposed to play a role in the progression of human immunodeficiency virus disease in Africa (33). Thus, in countries where parasite worms (such as helminths) are prevalent, the differentiation of Th2 cells induced by parasite antigens could produce cytokines that would affect the phenotype of T lymphocytes that recognize third-party antigens and hamper their differentiation into Th1 effector cells (34, 35).

Thus, important questions remain regarding the respective roles of environmental and host-related factors in the response to infection with M. tuberculosis, especially in Africa. A large and complex study is required in order to address these questions comprehensively. In this paper, we describe the approach taken in a multicenter study of tuberculosis that was recently initiated in West Africa. We outline the design of the study, describe the methodological issues that arose in the planning of the study, and indicate how we dealt with those issues. In a companion paper (36), we present in detail the investigation of genetic factors and discuss methodological aspects of the research. Although these papers deal with the specific aspects of investigation of the natural history of tuberculosis, we believe that the issues considered will be relevant to studies of the etiology and natural history of other infectious diseases, especially those in which risk factors for infection might be different from risk factors for disease—such as leprosy, African trypanosomiasis, and even hepatitis B, which can lead (in high-transmission areas) to hepatoma or cirrhosis decades after the original infection.

STUDY DESIGN

Principles

Our principal objectives were to determine the risk factors for active tuberculosis and to investigate the relative contributions of environmental and host-related factors. To do this thoroughly, we decided to adopt a design that included both a retrospective component and a prospective component, based on the recruitment of infectious cases with tuberculosis.

The study commenced in January 1999 and is being carried out in three countries in West Africa (The Gambia, the Republic of Guinea, and Guinea-Bissau), using consistent methodology and standardized questionnaires. Laboratory studies are being conducted in collaboration with European institutions. Baseline data on demographic factors and tuberculosis control in the three countries are shown in table 1. The general design of the study is shown in figure 1. The study design combines two case-control studies, a prospective household study, and family genetic studies (table 2). In
each country, newly diagnosed smear-positive cases with tuberculosis are recruited. Their households are visited, and demographic information is collected from all household members. The duration of the study allows 12–18 months for recruitment of index cases and controls and 2 years for follow-up of their household contacts. In each country, the study has been reviewed and approved by the national ethics committee.

**Case-control studies**

Two types of controls are being recruited. Within the household of each case, a healthy control is recruited to allow investigation of individual (host-related) risk factors while controlling for differences in household environment. This control is age matched to the case within 10 years. The host-related factors under investigation are: sex, Bacillus Calmette-Guérin vaccination, previous history of tuberculosis, infection with *M. tuberculosis*, smoking, alcohol intake, drug use, nutritional status, intercurrent infectious diseases (including human immunodeficiency virus infection), and conditions triggering a Th2-type lymphocyte response (such as parasitic infections, asthma, or atopy). A second control, also age matched to the index case within 10 years, is recruited at random from a nearby household for investigation of the effect of household factors (environmental and socioeconomic factors). These factors include: household size, number of people per room, type of house, hygiene, water supply, sanitation, presence of animals in the household, and socioeconomic status. These community controls also contribute to the genetic association study and provide a further resource for study of the effect of host risk factors, in addition to the household controls.

**Household cohort study**

In this study, a household is defined as members of an extended family living together in the same area and eating from the same pot. At baseline, extensive information is collected from all individuals who have lived in the household of the case and the household of the community control for more than 3 months, to assess their relatedness to the index case/control and their level of exposure to the case/control. Every member of the household is interviewed regarding past disease history, examined for the presence of a Bacillus Calmette-Guérin scar, skin-tested with tuberculin (2 tuberculin units of RT-23; Statens Serum Institut, Copenhagen, Denmark), and screened for signs and symptoms of tuberculosis. To avoid the influence of the “boosting” phenomenon when the tuberculin skin test is

### TABLE 1. Baseline information on demographic factors and tuberculosis control in three West African countries

<table>
<thead>
<tr>
<th></th>
<th>The Gambia*</th>
<th>Republic of Guinea†</th>
<th>Guinea-Bissau‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>1,380,000§</td>
<td>7,557,023§</td>
<td>1,096,224¶</td>
</tr>
<tr>
<td>Ratio of urban residents to rural residents</td>
<td>25:75</td>
<td>30:70</td>
<td>5:95</td>
</tr>
<tr>
<td>Bacillus Calmette-Guérin vaccination coverage (%)</td>
<td>94</td>
<td>76 countrywide</td>
<td>92 in Bissau</td>
</tr>
<tr>
<td>Tuberculosis case detection rate (per 100,000 population)</td>
<td>84 countrywide</td>
<td>70.2 countrywide</td>
<td>153 countrywide</td>
</tr>
<tr>
<td>Length of antituberculosis treatment (months)</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Outcome of treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured/completed treatment</td>
<td>76</td>
<td>78</td>
<td>50</td>
</tr>
<tr>
<td>Defaulted</td>
<td>14</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Died</td>
<td>6</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Other (failure, transferred out of study, unknown)</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Relapse rate (%)</td>
<td>2</td>
<td>2.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Prevalence of human immunodeficiency virus in the general population (%)</td>
<td>2.3</td>
<td>2</td>
<td>8.1</td>
</tr>
<tr>
<td>Prevalence of helminthiasis in the general population (%)</td>
<td>17</td>
<td>25</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

* Data were obtained from the National Leprosy/Tuberculosis Control Programme, Ministry of Health, Banjul, The Gambia, 1999.
† Data were obtained from the Programme National de Lutte Anti-Tuberculeuse, Conakry, République de Guinée, 2000.
‡ Data were obtained from the Programma Nacional de Luta contra a Lepra e a Tuberculose, Ministerio de Saude, Bissau, Guinea-Bissau, 1996.
Genetic and Environmental Risk Factors for Tuberculosis

FIGURE 1. General design of a multicenter study of tuberculosis risk factors in West Africa, showing the links between the case-control studies, prospective household cohort study, and family-based genetic studies. TB, tuberculosis; HH, household; TST, tuberculin skin test; TDT, transmission disequilibrium test; ASP, affected-sibling pair analysis.

The households of cases and controls are visited after 3, 6, 12, 18, and 24 months for detection of any incident case. During these visits, field-workers check for the presence of all persons initially recorded as being household members, record the names of those who have left or died, and assess the clinical condition of persons present. For detection of conversion, tuberculin skin testing is repeated in subjects who have previously had a negative response (<5 mm) 6 months after the first test has been performed (37). Field-workers also identify suspected cases of tuberculosis on the basis of the following characteristics: clinical signs and symptoms (cough for more than 3 weeks, fever, weight loss, night sweats, chest pain, hemoptysis); a tuberculin skin test response greater than 15 mm in diameter (38); and tuberculin skin test conversion over the first 6 months of follow-up. Persons with suspected tuberculosis are referred to the study physicians for clinical examination and further investigation: sputum smear and culture, chest radiograph, gastric lavage, bronchoscopy, and appropriate biopsy when extrapulmonary disease is suspected.

Immunologic studies

To evaluate the Th1/Th2 balance in tuberculosis, specific serologic markers of Th1 and Th2 cell activity are measured. On the basis of recent work, we decided to use immunoglobulin E, soluble CD30 antigen, and macrophage-derived chemokine as markers of ongoing Th2 activity in vivo (39, 40) and the product of lymphocyte activation gene-3 as a marker of Th1 activity (41). These markers of Th1/Th2 balance are measured in the cases, in household members, and in community controls at entry into the study, after 2 months of treatment, and at the end of treatment.

METHODOLOGICAL ISSUES

Case-control studies

Case definition and inclusion criteria. Cases are being recruited at major urban health centers in The Gambia, the Republic of Guinea, and Guinea-Bissau. All patients over age 15 years with newly detected smear-positive pulmonary tuberculosis who have been living at their current address for more than 3 months are eligible for inclusion in the study. Pulmonary tuberculosis must be confirmed by two consecutive sputum smears that are positive for acid-fast bacilli and positive culture. Informed consent is obtained prior to enrollment.

Selection of household controls. The choice of possible controls within each household is limited, despite the average household size's being 10–12. For families, the only eligible person in the required age range may often be the spouse, which results in “antimatching” on sex. We decided that the confounding effects of age were likely to be considerably greater than those of sex and that this disadvantage was worth accepting. We set no condition on the genetic relation between the case and the control. Any confounding effects of sex or familial relationship will be taken into account in the analysis, using conditional logistic regression.

Selection of community controls. A control household is selected by choosing a random direction from the case’s home (by spinning a pen in the air) and visiting the fifth dwelling on the right. If, as is common in Africa, several...
households share the same dwelling, field-workers select one household by drawing lots. The study is explained to members of the household, and if they agree to participate, workers select at random a healthy adult, matched to the case within 10 years of age, to serve as a control for the index case. In case of refusal or lack of a suitable control, the field-workers repeat the above procedure to select another household. If the household agrees to cooperate but the person selected is not present, an appointment is made for another visit.

The nature of the sampling process for external controls means that households rather than persons are selected with equal probability. This is appropriate, since external controls are selected mainly for the evaluation of household-level risk factors. However, a person in a small household will have a higher probability of being selected as a control than a person in a large household. We considered simple procedures designed to overcome this—for example, selecting a random household to start with, going from household to household until, say, 20 adults have been listed, and then selecting one at random. However, pilot studies showed the procedure to be too complex to implement effectively.

Matching the control with the case on household size and sex as well as on age would also have precluded the evaluation of these factors as risk factors.

**When a control develops tuberculosis.** Occasionally a control might become a case. Because of exposure, it is likely that this will be a household control rather than a community control. This subject will not be recruited into the case-control study as a case because of a lack of independence from the index case, but he or she will remain in the study as a control. In this situation, an analysis matched on time of selection will yield an unbiased estimate of relative risk, provided that this is constant over the study period (42).

**Cohort study**

**Case definition for secondary tuberculosis.** In all cohort studies, the outcome of interest should be clearly defined in order to avoid biased estimates of rates. In this study, the “secondary” cases that will develop within the households of index cases are more likely to occur among children (because of direct transmission’s leading to primary tuberculosis) or young persons (mainly because of exogenous reinfection) than among adults, for whom the time span between infection and development of disease might be much longer in the absence of specific factors such as human immunodeficiency virus infection (8, 9). To account for the difficulty of diagnosing tuberculosis in adults with smear-negative or extrapulmonary disease and in children (43, 44), we set up a certainty grading system that quantifies the confidence with which a suspected case can truly be said to be a case of tuberculosis, based on several published systems for adults (45–47) and children (48). Thus, depending on the presence and combination of defined signs and symptoms, cases of tuberculosis will be graded as “possible,” “probable,” or “certain.”

**Follow-up.** The duration and frequency of follow-up are based on the estimation that 5 percent of tuberculosis cases will develop within 2 years of infection (11, 12). Members of the households of the case and the community control are

<table>
<thead>
<tr>
<th>Study type</th>
<th>Study method</th>
<th>Objective/outcome</th>
</tr>
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<tbody>
<tr>
<td>Case-control study</td>
<td>Comparison of index cases with household controls</td>
<td>Investigation of host risk factors</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Comparison of index cases with community controls</td>
<td>Family history of tuberculosis</td>
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<tr>
<td></td>
<td></td>
<td>Investigation of environmental risk factors</td>
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<td></td>
<td>Investigation of host risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candidate genes (association study)</td>
</tr>
<tr>
<td>Household cohort study</td>
<td>Follow-up of members of households of index tuberculosis cases and community controls</td>
<td>Comparison of “exposed” families with “noneexposed” families</td>
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<tr>
<td></td>
<td></td>
<td>Relative risk of developing tuberculosis according to exposure and relatedness to the index case</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigation of host and environmental risk factors</td>
</tr>
<tr>
<td>Family-based genetic studies</td>
<td>Transmission disequilibrium test</td>
<td>Risk associated with having an allele of a candidate gene; fine mapping of the candidate region</td>
</tr>
<tr>
<td></td>
<td>Affected-relative linkage analysis</td>
<td>Coarse mapping of the genome or of the candidate region</td>
</tr>
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</table>

**TABLE 2. Design components of a study of tuberculosis risk factors in West Africa, 1999**
followed up regularly for detection of any suspected case of tuberculosis. To encourage self-referral of household members in the event of suspected tuberculosis, study participants are actively trained in detecting the signs and symptoms of the disease, and a card permitting free access to the study clinic is provided to them.

**Development of tuberculosis and proximity to the index case.** In addition to investigating the effects of specific risk factors on the development of tuberculosis, the rate of developing the disease will be estimated within the cohort of household contacts of cases, according to the degree of exposure of the individual to the index case and his or her genetic proximity to the index case. The degree of exposure is assessed through measurement of the contact’s geographic proximity to the case within the household and the case’s infectiousness. This infectiousness is estimated through the “bacterial load” of the case’s expectoration, measured by the standard semiquantitative assessment of the initial sputum smear positivity, the frequency of cough measured over 24 hours using a specifically designed “cough meter,” and the presence of a cavity on the patient’s chest radiograph. The degree of genetic proximity is measured by the coefficient of relationship, the fraction of identical genes shared by descent by two individuals (49). The ratio of the disease rate in siblings of the case living in the household to the disease rate in unrelated members of the household will provide an indication of the sibling recurrence risk ratio, \( \lambda_s \) (50), although this is usually measured by comparing all siblings with the general population.

**Immunologic studies**

Use of the matched triplets constituted by the case, the exposed contact, and the healthy community control provides a unique model for studying the natural history of tuberculosis, representing various stages of the infection from exposure to disease. Comparison of Th1/Th2 indicators in the sera of 1) community controls with no known recent exposure to tuberculous infection, 2) recently exposed healthy individuals, and 3) smear-positive cases allows one to “reconstruct” the natural history of tuberculosis in individuals without embarking on long prospective studies. Follow-up of cases during treatment allows investigation of the impact of treatment on Th1/Th2 markers and the association of changes in cases’ serum concentrations with disease persistence or healing. Comparison of in-vitro responses to defined antigens in these triplets can also reinforce analysis of the contribution of host immune response to the natural history of tuberculosis. Nested case-control studies investigating in-vitro response to defined *M. tuberculosis* antigens will be conducted in a subsample of cases and controls (51).

**Sample size calculation**

The sample size required to detect a given odds ratio follows a U-shaped distribution with respect to the prevalence of the risk factor under investigation. Hence, the recruitment of 800 cases and similar numbers of controls will provide at least 80 percent power to detect an odds ratio of 1.6 for any risk factor (genetic, immunologic, or environmental) with a prevalence between 10 percent and 85 percent in the controls and to detect an odds ratio of 1.4 for any factor with a prevalence between 20 percent and 70 percent.

The number of secondary cases expected in this study is not large. The incidence of active tuberculosis in the general population is estimated to be approximately 0.1 percent per year (2, 11). In the control households, with an average of 10 members per household, follow-up of 800 households for 2 years will be expected to yield only 13 cases, assuming 20 percent loss to follow-up. Preliminary results indicate an incidence among members of case households of 0.8 percent per annum, such that we can expect to detect approximately 92 secondary cases in these households; this should be sufficient to estimate the effects of specific factors on development of tuberculosis in contacts. Lastly, since most of the secondary cases will be relatives of the index cases, they will contribute one affected pair to the allele-sharing study.

**DISCUSSION**

Tuberculosis is a multifactorial disorder in which the environment interacts with host-related factors, contributing to the overall phenotype. Improved understanding of 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 on the development of disease, will have strong implications for tuberculosis control and prevention (7); increased insight can help us redirect intervention efforts, such as contact tracing and contact prophylaxis. It may contribute usefully to research on new vaccines against tuberculosis through a better understanding of host immune response (52, 53), and the identification of genes that affect risk of disease can be useful in generating new vaccine candidates. Lastly, the establishment of cohorts of tuberculosis patients and their contacts may provide useful baseline data for the development of future phase III vaccine trials.

The present study design combining the case-control method and the prospective household contact method may be complex, but it offers the advantage of assessing together the roles of environmental, immunologic, and genetic factors, both prospectively and retrospectively (36). In addition, it allows differentiation between the risk of becoming infected and the risk of developing disease after infection, adjusting for tuberculin reactivity and/or history of Bacillus Calmette-Guérin vaccination—something that has not always been possible in former studies. The innovative aspect of assessing the triplet formed by the case, the exposed contact, and the healthy community control provides an opportunity to investigate protective immunity to tuberculosis in humans, and recruitment of contacts offers a framework for additional studies on immunologic markers of tuberculosis (51).

However, this design entails some limitations. The workload of follow-up is high, especially in the control families, where the risk of developing tuberculosis is likely to be very small. In addition, as in all cohort studies, validity depends
on the capacity to detect all events of interest (here, the “secondary” cases) that occur within the study population. This depends on the logistics of the study but also on the case definition. Since follow-up in our study is initially restricted to 2 years, we are more likely to detect “primary” tuberculosis among child contacts (11, 54). The clinical picture of “primary” tuberculosis is quite different from that of the “reactivated” or “reinfected” form of the disease, and the pathophysiologic pathways might differ as well (55). Therefore, at the time of analysis, it will be important to quantify the certainty of the diagnosis. In many countries, preventive therapy with isoniazid is recommended for children under age 5 years who are exposed to an active case (56). However, most countries in the developing world do not implement chemoprophylaxis of contacts because of the cost involved and the fear that noncompliance might increase drug resistance. For that reason, in this study, follow-up of contacts in the case households will be intensive, and the criteria used to detect tuberculosis in children are very sensitive.

There are major differences in the distributions of tuberculosis infection (as measured by tuberculin surveys) and disease (as measured by case-notification rates) in industrialized and nonindustrialized countries (2, 11). However, research on environmental factors affecting the incidence of infection/disease carried out over the past 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, increased case notification in the early 1990s triggered investigation of individual risk factors for identification of high-risk groups in which to target control activities (57). This led to a rapid decline in notification for tuberculosis in some areas (58). However, this type of investigation has not been extensively carried out in developing countries. While we are waiting for new vaccines to be developed and tested, investigation of the respective roles of environmental and genetic factors may provide new insights that will improve tuberculosis control through better prevention and care adapted to specific situations (7).

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