Prevalence of Tuberculosis Infection in BCG-Vaccinated and Unvaccinated Mediterranean Schoolchildren

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OBJECTIVE: To determine the prevalence of tuberculous infection in schoolchildren in the province of Malaga, Spain, and to evaluate its relation to sociodemographic variables.

POPULATION AND METHODS: Tuberculin skin tests were used to screen 6-year-olds in their first year of primary school in this cross-sectional study of the prevalence of infection, with calculation of 95% confidence interval (CI). Children who had not been vaccinated against tuberculosis at birth were considered to have a positive test result if they had an induration of ≥5 mm. Those who had received bacillus Calmette–Guerin (BCG) vaccination at birth were considered to have a positive test result if they had an induration size of >10 mm or >15 mm, depending on whether they came from a country with high or low prevalence of tuberculosis, respectively.

RESULTS: The prevalence of infection in the group of unvaccinated children was 1.16% (95% CI, 0.69%-1.63%). No statistically significant differences were found for any of the sociodemographic variables analyzed. The prevalence of infection in the BCG-vaccinated children was 6.66% (95% CI, 5.55%-7.77%).

CONCLUSIONS: The prevalence of tuberculosis infection in our area is slightly higher than that reported after other studies conducted in Spain. This could indicate that tuberculosis continues to be a public health problem in the province of Malaga. Infection in the subgroup of BCG-vaccinated children, however, was lower than that observed in studies of immigrants in Spain who had been immunized at birth. This is probably because the majority of immigrants in our area come from countries with a low incidence of tuberculosis.

Key words: Tuberculosis. Prevalence. Sociodemographic variables.

Prevalencia de infección por tuberculosis en una población escolar mediterránea (con y sin vacunación antituberculosa)

OBJETIVO: Conocer la prevalencia de infección por tuberculosis en la población escolar de la Costa del Sol y valorar la relación de variables sociodemográficas con la prevalencia de infección tuberculosis.

POBLACIÓN Y MÉTODOS: Se trata de un estudio de corte transversal, en el que se realizó cribado tuberculínico a los niños de primer curso de primaria (6 años). El índice epidemiológico analizado fue la prevalencia de infección, con su intervalo de confianza (IC) del 95%. Se consideró positivo a la prueba de la tuberculina a todo niño que no había recibido la vacuna antituberculosa al nacer y que presentaba una induración igual o superior a 5 mm. En el subgrupo vacunado contra la tuberculosis al nacer se consideró positivos a los niños con induración superior a 10 mm o a 15 mm, según procediesen de países con elevada o baja prevalencia de tuberculosis, respectivamente.

RESULTADOS: La prevalencia de infección obtenida en el grupo de no vacunados fue del 1,16% (IC del 95%, 0,69-1,63%). No se encontraron diferencias estadísticamente significativas entre las variables analizadas. La prevalencia de infección en el subgrupo de vacunados fue del 6,66% (IC del 95%, 5,55-7,77%).

CONCLUSIONES: La prevalencia de infección tuberculosis en nuestra zona es ligeramente elevada en comparación con la observada en otros estudios realizados en nuestro país, lo que podría indicar que la tuberculosis sigue siendo un problema de salud pública en nuestra provincia. No ocurre así con el subgrupo de vacunados contra la tuberculosis, en el que, comparado con los de otros estudios realizados en nuestro país entre la población inmigrante vacunada al nacer, la prevalencia es baja, probablemente debido a que la mayoría de inmigrantes de la Costa del Sol proviene de países con baja incidencia de la enfermedad.

Palabras clave: Tuberculosis. Prevalencia. Variables sociodemográficas.

Introduction

The prevalence of tuberculosis has increased worldwide in the last 30 to 40 years according to several organizations, including the World Health Organization, which has...
estimated that approximately a third of the world’s population is infected by the disease. Tuberculosis has been particularly widespread in Spain for decades and current prevalence figures continue to be inconsistent with the country’s level of development. Nonetheless, the number of declared cases did begin to decrease gradually in the mid 1990s and this trend has persisted into recent years.

Another factor of concern in Spain is the high rate of tuberculosis infection in children compared to other countries in western Europe, given that it is not the result of reactivation of an old focus of infection but rather of recent primary infection, demonstrating the recent introduction of the tuberculosis bacillus into the community. A series of tuberculin test survey studies have been conducted among Spanish schoolchildren in recent years in order to assess the prevalence and epidemiological features of tuberculosis in different geographical areas. In the only study of this kind conducted in the province of Malaga and published in 1957, a very high tuberculosis prevalence of 62.22% was reported. To the best of our knowledge, this is the most recent information available on the prevalence of tuberculosis infection in schoolchildren in Malaga or anywhere else along the Andalusian coast. The main aim of the present study was therefore to determine the prevalence of tuberculosis infection in bacillus Calmette–Guerin (BCG)-vaccinated and unvaccinated schoolchildren in the Costa del Sol region of Spain. A secondary aim was to assess the relation between infection prevalence and a range of sociodemographic variables.

Population and Methods

Study Design and Population

We conducted a cross-sectional study of schoolchildren in their first year of primary school in the first semester of 2004. The majority of the children were 6 years old. Participants were recruited from public, private, and publicly subsidized schools in 10 different towns and cities in the health district served by Hospital Costa del Sol (western coast of the province of Malaga).

Included were all children in their first year of primary school at the time of the study with the exception of those whose parents did not sign the informed consent form and those who had a history of treatment for tuberculosis infection or disease.

Procedures

Meetings were held with the school principals and the parents of the children involved during the months of January and February 2004 to explain the study objectives and methodology. Each child was given a notebook containing 3 pages (a description of the study, a questionnaire, and an informed consent sheet).

During February and March of the same year, 4 nurses visited the participating schools and performed the tuberculin skin test on all the children who were present on the day of the test and whose parents had signed the consent form. The test was performed following the Mantoux intradermal injection method, whereby a 2-TU dose of purified protein derivative RT-23 (Evans; UCB Farma, Barcelona, Spain) was injected into the inner forearm and measurements taken at 48 to 72 hours. Indurations were measured using the method described by Sokal to reduce the rate of interindividual error.

Positive Test Result Criteria

The following criteria were used to determine positive skin test results. In children who had not been vaccinated against tuberculosis at birth, an induration of 5 mm or larger was considered to be a positive test result, regardless of whether or not the child had been in recent contact with a sputum-positive patient. Three induration size categories were used to classify positive reactions in children who had received BCG vaccination at birth: a) 5 mm or larger if the child had been in recent contact with an infected patient or had clinical or radiological signs of tuberculosis, b) larger than 10 mm if the child had had no known contact with an infected patient and had been born in a country with a high prevalence of tuberculosis, and c) 15 mm or larger if the child had had no known contact with an infected patient and had been born in a country with a low or normal prevalence of tuberculosis. We applied these criteria because the chance of a positive tuberculin skin reaction being a true rather than a false positive in any given population is influenced by the prevalence of Mycobacterium tuberculosis infection in that population. The tuberculin skin test therefore has a low positive predictive value in countries with a low prevalence of tuberculosis infection, making it necessary to increase the maximum induration threshold (to ≥15 mm) to avoid the risk of false positives. In countries with a high rate of infection, the test has greater predictive power and a threshold of 10 mm is considered sufficient.

Children with an induration of 5 mm or larger were examined at the outpatient clinic at our hospital. Clinical assessment included history taking, physical examination, and posteroanterior and lateral chest radiographs. Chest radiographs were analyzed by 2 radiologists, and a follow-up computed tomography chest scan was performed if considered necessary. Patients with normal radiographic findings were diagnosed with latent tuberculosis infection and prescribed secondary chemoprophylaxis. Those with abnormal radiographic findings were diagnosed with tuberculosis, and gastric washings were obtained to perform microbiological smears and cultures. These patients were administered triple drug therapy. A contact investigation was conducted within the families of all children with an induration of 5 mm or larger.

Statistical Analysis

To calculate the smallest sample size necessary for estimating prevalence, we analyzed the results of studies performed in Spain in the preceding 10 years involving similar populations in the same age group. Based on a likelihood of 0.4% according to the null hypothesis (smallest value found) and of 1.18% according to the alternative hypothesis (highest value found), a significance level of .05, and a statistical power of 95%, we determined that we needed to study at least 1434 children. Assuming a maximum allowable loss of 33%, this figure was raised to 1912 children.

We assessed epidemiological indicators (prevalence) separately in children who had been vaccinated against tuberculosis at birth and those who had not. Our reasoning was that because the majority of BCG-immunized children had been born in countries other than Spain, our findings for this group would provide a better picture of prevalence rates for those countries than for Spain (the main object of our study).

The sociodemographic variables analyzed included type of school and municipality, history of tuberculosis vaccination (information obtained via questionnaire), place of birth of children and parents, educational level of parents, number of persons
residing in the child’s household, and the time between the
tuberculin skin test and the test reading (48 or 72 hours).

Variables were compared using the \( \chi^2 \) test and statistical
significance was set at a level of \( P < 0.05 \); 95% confidence
intervals (CI) were calculated for the estimates of proportions
(prevalence rates). Participants and nonparticipants were
compared, and data were analyzed using the SPSS software
package, version 11.5.

**Results**

**Description of the Population Sample**

Informed consent was obtained from the parents of 2117
(62.4%) of the 3391 children in their first year of primary
school at the time of the study in 2004. The final number of
children who completed the study (ie, who attended
school on the day of the test and underwent tuberculin
skin testing) was 1991 (58.7%). Of these, 180 had been
vaccinated against tuberculosis at birth and 1811 had not.
No significant differences were found between the
participant group (children analyzed) and the nonparticipant
group (children for whom consent was not obtained) with
regard to any of the sociodemographic variables analyzed.

**Unvaccinated Group**

Twenty-one of the children who had not been vaccinated
against tuberculosis at birth had a positive skin test result
(induration of 5 mm or greater) (Table 1). This corresponds
to a prevalence of infection of 1.16% (95% CI, 0.69%-1.63%). Sex was the only sociodemographic variable for
which there was a statistically significant difference between
groups (Table 2). Of the 21 children with a positive skin
test result, 2 were diagnosed with active tuberculosis
following examination of their radiographs. In addition,
in the analysis of gastric washings for \( M \) \( \text{tuberculosis} \),
1 of these 2 children had a positive finding by polymerase
chain reaction; that result was not confirmed by culture,
however. The prevalence of tuberculosis infection was
therefore 0.11% in the entire group and 9.5% in the
subgroup of children with positive tuberculin skin test
results.

A contact investigation was conducted in 14 families
and positive Mantoux reactions were found in 6 of these.
In total, 10 household contacts had a positive tuberculin
skin test result. Of these, 3 (all adults) were identified as
the index cases, or sources of infection. Two were relatives
of the 2 children diagnosed with active tuberculosis and thus
accounted for 14.3% of the total number of unvaccinated schoolchildren with a positive tuberculin
skin test result, 100% of children with active tuberculosis,
and only 5.26% of children diagnosed with latent
tuberculosis infection. Contact investigations were not
conducted at the schools.

**Vaccinated Group**

Twelve of the children who had been vaccinated against
tuberculosis at birth had a positive tuberculin skin test
result. Three of these had an induration larger than 14 mm
and 9 had an induration of between 11 and 14 mm (Table 1). All of the children in the second group had been born in
countries with a high prevalence of tuberculosis. These
figures indicate a prevalence of infection of 6.66% (95% CI, 5.55%-7.7%) in this subgroup. No statistically
significant differences were found for any of the sociodemographic variables analyzed (Table 2), and we
found no evidence of disease in any of the vaccinated
children.

**Discussion**

In our study of tuberculosis infection in schoolchildren
along the Costa del Sol (western coast of the province of
Malaga), we detected a prevalence of 1.16% in the group
of unvaccinated children and of 6.66% in the group of
vaccinated children. No statistically significant differences
were found for any of the sociodemographic variables
analyzed.

The relatively high nonparticipation rate (40%) observed
could have several explanations. Firstly, the duration of
the study (just 2 months) might have provided insufficient
time to properly inform and involve parents, and secondly,
the tuberculin skin tests were only held on 1 day at each
school, meaning that children who were absent on that
day were excluded from the study. Although this could
have introduced selection bias, we did not find any
statistically significant differences between the children
in the participant and the nonparticipant group, indicating
that our sample was indeed representative of the study
population. In an effort to prevent bias during the induration
classification stage, all skin reactions were measured by
specially trained nurses. We chose 5 mm as the threshold
size for the unvaccinated group. Not only is this the size
recommended in the consensus guidelines for the control
of tuberculosis in Spain drawn up in 1992, but it has also
been used in similar studies in Spain in the past 10 years,
allowing us to compare our results with those from other
areas of the country. This is why we did not use the
treshold size of 10 mm recommended by the Spanish
Society for Pediatric Infectology (SEIP) in 2003.

A number of other studies analyzing the prevalence
of tuberculosis infection in children aged 6 years have
been conducted in Spain since the 1990s (Table 3). Only
2 of these studies, however, found a prevalence that was
similar to or slightly higher than ours (1.16%). All the
others found a lower prevalence, which suggests that
tuberculosis might be a more serious public health

<table>
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<tr>
<td></td>
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</tr>
<tr>
<td>&lt;5</td>
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<td>5-10</td>
<td>13</td>
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<tr>
<td>11-14</td>
<td>3</td>
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problem in our area than in other parts of Spain. The only other study of tuberculosis prevalence in the province of Malaga was published in 1957. As is to be expected given the high rates of tuberculosis infection in Spain at the time, it found a prevalence of 62.22% among children and of 50% among children aged 6 years old. It is impossible to compare the results of that study to ours, however, as it was conducted many years ago and at a time when tuberculosis was particularly widespread in Spain. It is therefore impossible to determine if

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<tr>
<td>72 h</td>
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</table>
tuberculosis prevalence in our area has increased or decreased with respect to recent years.

The fact that we found no statistically significant differences in any of the sociodemographic variables analyzed might reflect the highly homogeneous nature of the population in the Costa del Sol area, where social exclusion is almost imperceptible.

Only a few studies have analyzed tuberculosis prevalence in BCG-immunized children in Spain in the last 15 years as the routine use of this vaccine was discontinued throughout Spain in 1987 (except in the Basque country, where it is still used). One such study, performed in Albacete in 1992, found a prevalence of 3.27% in a group of 6-year-old children (positive skin test results were determined by an induration threshold of 14 mm or larger). A later study, conducted in 1999 and 2000 in an area of Barcelona with a high rate of immigration, found a prevalence of 2.1% in children aged 5 to 10 years using the same threshold. We used 2 induration sizes in our study: larger than 10 mm for children aged 5 to 10 years using the same threshold.18 We considered that the predictive value of the tuberculin skin test is closely related to the prevalence of infection in the population being studied. The prevalence of infection in our group of BCG-vaccinated children was 6.66%. If we had followed the same threshold as that used in the above studies, however, prevalence would have fallen to 1.66% as only 3 children in our group had an induration of 14 mm or larger. The fact that we found a lower prevalence of tuberculosis infection in vaccinated children than did studies conducted in other areas might indicate that immigration is probably not the reason for the higher rate of tuberculosis infection in this western coastal area near Malaga (it should be remembered that the majority of vaccinated children are immigrants). This is probably because most of the immigrants in our area are from developed countries that have a much lower prevalence of tuberculosis than Spain. We did not find statistically significant differences between the groups for either the children’s or the parents’ country of origin but this might be due to a lack of statistical power caused by the small number of children in the vaccination subgroup. On analyzing the prevalence of infection by geographical area for the children with a positive tuberculin skin test, we found the following rates: western Europe, 2.1%; eastern Europe, 15.4%; and Latin America, 9.1% (Table 2).

In conclusion, the prevalence of tuberculosis infection in unvaccinated schoolchildren along the western coast of the province of Malaga is slightly higher than that of other areas of Spain. The prevalence of infection in BCG-immunized children (the majority of whom were born in countries other than Spain) is, in contrast, lower (based on findings from other studies that have analyzed prevalence in vaccinated children). We found no statistically significant differences between the 2 groups for any of the sociodemographic variables analyzed. We should not forget, however, that our findings are for 2004 only. It would therefore be desirable to conduct other studies in the same area and in other areas of the province to confirm our findings and assess the current trends of tuberculosis infection.

Acknowledgments

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