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Study of Tuberculosis Outbreaks Reported in Catalonia, 1998-2002

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OBJECTIVE: To analyze the characteristics of tuberculosis outbreaks declared under vigilance programs in Catalonia.

METHODS: Descriptive study of outbreaks from 1998 through 2002 for which reports were available. An outbreak was defined as 3 or more associated cases appearing within a year. For 2 health care regions, outbreaks for which there were full surveillance reports with contact tracing were compared to outbreaks identified but which had not been fully reported.

RESULTS: Twenty-seven outbreaks were analyzed. Nineteen (70%) occurred within families. A total of 22 outbreaks were declared upon identification of the true index case and 5 upon detection of secondary cases. The mean annual incidence of outbreaks was 0.40/100 000 inhabitants.

Most cases were in males 16 to 40 years of age and involved cavitary lesions and a clinically significant diagnostic delay. Twenty-seven outbreaks caused 69 secondary cases.

A longer diagnostic delay was seen to correspond to a larger number of secondary cases (*P*=.08). In the 2 health care regions analyzed, full surveillance reports with contact tracing were issued for 2 of the 14 outbreaks detected (14.4%).

CONCLUSIONS: Tuberculosis outbreaks are common but investigative follow-up is scarce. The size of the outbreak is related to the length of diagnostic delay. Rapid diagnosis, contact tracing, and the issuance of a public health report should be priorities in all outbreaks detected.

Key words: *Disease outbreaks. Tuberculosis. Diagnosis, delayed. Secondary cases. Contact tracing.*

Estudio de los brotes de tuberculosis que han generado informes epidemiológicos en Cataluña (1998-2002)

OBJETIVO: Analizar las características de los brotes de tuberculosis (TB) estudiados por los servicios de vigilancia epidemiológica de Cataluña.

MÉTODOS: Estudio descriptivo de los brotes de 1998-2002 que disponían de informe epidemiológico. Se definió como brote epidémico cuando había 3 o más casos asociados en un año. En 2 regiones sanitarias se compararon los brotes detectados con los que además tenían informes.

RESULTADOS: Se analizaron 27 brotes y la mayoría (n = 19; el 70%) ocurrió en el ámbito familiar. Un total de 22 brotes fueron declarados a partir del caso índice auténtico y 5 a partir de un caso secundario. La incidencia media anual de brotes fue de 0,40/100.000 habitantes. La mayoría fueron generados por varones de 16 a 40 años, con lesiones cavitarias y un importante retraso diagnóstico. Los 27 brotes provocaron 69 casos secundarios. Se observó que a mayor retraso diagnóstico correspondía mayor número de casos secundarios (p = 0,08). En las 2 regiones sanitarias analizadas sólo se realizó informe epidemiológico en 2 de los 14 brotes detectados (14,4%).

CONCLUSIONES: Los brotes de TB son frecuentes pero poco investigados, y el retraso diagnóstico se asoció al tamaño del brote. Se deben priorizar el diagnóstico rápido de los enfermos, el estudio de contactos y la realización de un informe sanitario en cada brote detectado.

Palabras clave: *Brotes epidémicos. Tuberculosis. Retraso diagnóstico. Casos secundarios. Contactos.*

Introduction

Tuberculosis is a communicable disease whose spread depends on the presence of a sputum-positive case.

The development of an outbreak is facilitated by various factors, among them the degree of sputum positivity, frequency and continuity of exposure of subjects who will develop secondary infections, overcrowding, prevalence of reduced infection in contacts, subject age, socioeconomic characteristics, natural immunity, diagnostic delay and/or

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delayed treatment, lack of adherence, and human immunodeficiency virus (HIV) infection in contacts.[1-6]

A tuberculosis outbreak, or minor epidemic, has traditionally been defined by at least 2 secondary cases generated by a single index case,[7] although an outbreak in most transmissible diseases is usually defined as a space-time cluster of new cases and/or infections generated by a source.[8,9] Recently, the Spanish national epidemiological vigilance network defined a tuberculosis outbreak as the appearance of 1 or more cases generated by the same index case over the period of a year following diagnosis of the index case.[10]

Various articles have been published in recent years on particular outbreaks, generally related to schools, households, hospitals, care facilities for the elderly, or penitentiaries,[5,11-14] but no population-based studies have appeared.

The aim of this study was to analyze the nature of tuberculosis outbreaks investigated in Catalonia, Spain, and of the index cases that generated them, with a view to improving knowledge of factors that influence the appearance of outbreaks in our community and broaden measures of prevention and control.

Methods

Tuberculosis outbreaks investigated by epidemiological surveillance services were reviewed by examination of epidemiological reports for the period 1998-2002 in Catalonia, a Spanish autonomous community with a population of 6 343 110 inhabitants in 2002 and a total of 1698 cases of tuberculosis, for an incidence rate of 26.7/100 000 inhabitants.[15]

An outbreak was defined as 3 or more related cases of tuberculosis identified within a year. A case was defined by 2 criteria, both of which had to be met: *a)* presence of signs or symptoms indicative of tuberculosis involving any anatomical site in the absence of any other disease to which they could be attributed after a complete diagnostic assessment, and *b)* prescription of a standard antituberculosis treatment, usually 3 or more drugs. Probable latent tuberculosis infection was defined in the context of an outbreak if there was an induration of at least 5 mm after a tuberculin skin prick in the absence of disease symptoms.[15-17] The initial index case was defined as the first case reported for an outbreak, and the ultimate, or true, index case was the one eventually identified as the true focus in accordance with time of onset of symptoms, sputum microscopy, radiographic lesions, and results of contact tracing. Subsequent cases of tuberculosis generated by the true index case were classified as secondary cases.

Data collected for each outbreak were date first reported, reporting health care center, health care region, and initial and true index cases. Moreover, for each case, we recorded sex, age, date of onset of symptoms, treatment, number of household and nonhousehold contacts, country of origin, and diagnostic evidence (symptoms, microbiology, radiography, etc). Index and secondary cases were classified according to anatomical location of disease as pulmonary (cavitating or noncavitating) or extrapulmonary. Cases were also classified according to site of transmission as family, workplace, school, and community. The last classification was subdivided into geriatric, sports, leisure, or other facilities. Contacts were classified as household or nonhousehold, and the latter as workplace, school, or leisure.

For 2 health care areas (Barcelona City and Central Catalonia) we retrospectively investigated all outbreaks detected during the study period in order to determine if full surveillance reports were issued and to compare data. To accomplish the comparison, we contrasted the data we collected with those provided by the tuberculosis prevention and control programs of Central Catalonia and of Barcelona City (tuberculosis unit of the Drassanes facility).

Statistical Analysis

The diagnostic delay in smear-positive cases was calculated by the difference between the dates of start of treatment and onset of symptoms. Delay was recorded in 3 categories: *a)* fewer than 35 days, *b)* 36 to 70 days, or *c)* 71 days or longer. The secondary case rate was calculated by multiplying the number of such cases by 100 and dividing by the number of contacts exposed to each index case. Descriptive statistics for outbreaks were compiled and analyzed with the SPSS software for Windows. Qualitative variables were compared with the χ^2 test. The correlation between secondary cases and diagnostic delay in the index case was analyzed by linear regression (number of secondary cases in the outbreak plotted against the number of days of delay).

Results

Twenty-seven outbreaks were analyzed. Transmission took place in the family in 19 (70%) cases, the community in 6, the school in 1, and the workplace in 1. A total of 22 outbreaks were declared upon identification of the true index case and 5 upon detection of secondary cases. The mean annual incidence rate was 0.40 outbreaks/100 000 inhabitants, with variations by health care region. The highest incidence was 2.02/100 000 in Lleida and the lowest was 0/100 000 in Tarragona and Central Catalonia (Table 1). The 27 outbreaks involved 69 secondary cases, of which 39 (56.52%) were males and 30 (43.47%) females (Table 2). A trend toward increasing incidence was observed when evolution over time was analyzed: 3 outbreaks in 1998 and 1999, 5 in 2000, 8 in 2001, and 7 in 2002. The health care areas of Barcelona City and Central Catalonia saw only 2 outbreaks with surveillance reports (14.4%) out of 14 detected outbreaks. The 2 surveillance reports were for the area of Barcelona City, giving a rate of 25% (2 out of 8) in that area; no surveillance reports were issued in Central Catalonia (0 out of 6 outbreaks detected).

Seventeen initial index cases were cavitating pulmonary tuberculosis, 7 were noncavitating, 2 were pleural, and the remaining cases were in lymph nodes. However, when the analysis was repeated for true index cases, all had pulmonary tuberculosis. Sixty-two percent (16/27) of the true index cases were males, 85% were between 16 and 49 years old, and 73.1% had cavitary lesions. All those percentages were lower in the secondary cases (Table 2). Two index cases also had acquired immunodeficiency syndrome (AIDS) and none were immigrants, although there were immigrants among the secondary cases.

A longer diagnostic delay was seen to correspond to a larger number of secondary cases (P=.08) (Figure). In

TABLE 1
Incidence Rates for Tuberculosis Outbreaks Investigated and Cases in Outbreaks, by Health Care Areas in Catalonia, Spain, 1998-2002

Health Care Area	Population, 2001	No. of Outbreaks	Incidence Outbreaks/ 100 000 inhabitants	No. of Cases in Outbreaks	Incidence Cases/ 100 000 inhabitants
Barcelona City	1 503 884	2	0.13	7	0.46
North Barcelona-Maresme	708 118	3	0.42	6	0.84
Girona	552 855	6	1.26	24	5.06
Lleida	346 380	7	2.02	25	7.50
Tarragona	468 540	0	0	0	0
South Coast	1 221 273	8	0.65	26	2.12
Tortosa	136 115	1	0.73	8	5.87
Central Catalonia	1 405 945	0	0	0	0
Total	6 343 110	27	0.40	97	1.52

TABLE 2
Distribution of True Index and Secondary Cases by Tuberculosis Type and Anatomical Location in Outbreaks in Catalonia, Spain, 1998-2002

Anatomical Location/Types	True Index Cases (n=27)			Secondary Cases (n=69)		
	Men	Women	Total	Men	Women	Total
Lung, cavitating	13	7	20	7	3	10
Lung, noncavitating	4	0	4	26	25	51
Pleura	0	1	1	4	2	6
Lymph nodes	0	1	1	2	0	2
Lung, cavitating and genitals	1	0	1	0	0	0
Total	18	9	27	39	30	69

44% (11 index cases) of the 25 outbreaks for which it was possible to calculate the time between onset of symptoms and treatment, delay was between 36 and 71 days; for 6 (24%) the delay was 71 days or longer; and for 6 it was under 35 days. In the 8 outbreaks with a delay under 35 days, the mean number of cases was 2.62. The mean was 2.81 in the 11 outbreaks with delays between 36 and 70 days, and 2.83 in outbreaks with delays over 71 days. The differences were not significant.

Certain features of the outbreaks that are of considerable epidemiological interest are shown in Table 3.

Outbreak 4, for which the site of transmission was the community, occurred on a football team. The index case was a 26-year-old player with pulmonary tuberculosis. Contact tracing revealed 2 cases on the team: the first aged 20 years with pleural disease and the other aged 18 years with lung disease. Three cases of latent infection were also detected among the 27 contacts traced.

Outbreak 12 affected 2 families. The initial index case was a child of 4 months, and tracing led to nonhousehold contacts and to a school. The true index case (a 28-year-old adult with cavitary lesions) was located in the school, where another secondary case (a 7-year-old boy with noncavitary radiographic signs) was found. In total, 32 contacts (18 school children and 14 families) were traced and 2 cases of disease and 10 of latent infection were identified.

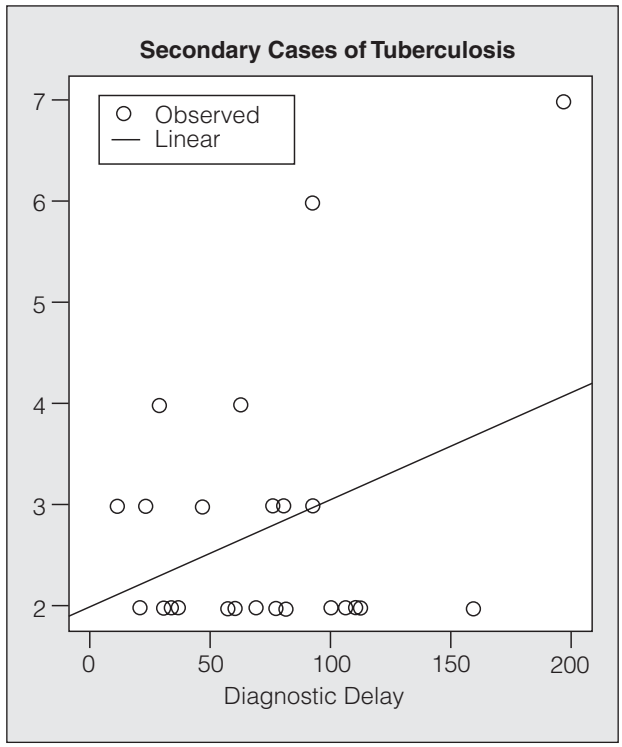

Figure. Linear relationship between diagnostic delay (days until diagnosis of the true index case) and the number of secondary cases in the tuberculosis outbreaks studied from 1998 through 2002. Secondary tuberculosis cases are to the total number of cases caused by each outbreak over time.

TABLE 3
Distribution and Characteristics of Tuberculosis Outbreaks Investigated in Catalonia, Spain, 1998-2002

Case	Site of Transmission	Index Case			Secondary Cases	Contacts	Secondary Case Rate, %*
		Age, y	Sex	Type			
1	Workplace	25	Female	Noncavitating	2	193	1.03
2	Family	26	Male	Cavitating	4	14	28.57
3	Family	41	Male	Cavitating	3	4	75.00
4	Community	26	Male	Noncavitating	2	27	7.40
5	Family	21	Male	Cavitating	3	82	3.66
6	Community	38	Female	Noncavitating	3	40	7.50
7	Escolar	43	Male	Noncavitating	2	77	2.59
8	Community	39	Male	Noncavitating	6	20	30.00
9	Family	25	Male	Cavitating	2	9	22.22
10	Community	66	Male	Cavitating	4	8	50.00
11	Family	28	Male	Cavitating	3	3	100.00
12	Family	28	Male	Cavitating	2	32	6.25
13	Family	39	Male	Noncavitating	5	27	18.51
14	Family	20	Female	Cavitating	2	58	3.44
15	Family	62	Male	Noncavitating	2	6	33.33
16	Family	41	Male	Cavitating	2	2	100.00
17	Family	29	Female	Cavitating	2	3	66.67
18	Community	41	Female	Cavitating	3	170	1.76
19	Family	45	Male	Cavitating	2	5	40.00
20	Family	33	Female	Cavitating	2	12	16.66
21	Community	38	Male	Cavitating	7	30	23.33
22	Family	45	Male	Cavitating	2	11	18.18
23	Family	34	Female	Cavitating	3	53	5.66
24	Family	34	Female	Cavitating	2	63	3.17
25	Family	56	Male	Cavitating	2	7	28.57
26	Family	28	Female	Cavitating	2	15	13.33
27	Family	51	Male	Noncavitating	3	15	20.00

*The secondary case rate is calculated by multiplying the number of secondary cases of tuberculosis by 100 and then dividing by the number of contacts.

Outbreak 13 occurred in a family and included 5 cases of multidrug-resistant tuberculosis. The first case found was in a 39-year-old male with AIDS and miliary tuberculosis that was resistant to isoniazid, rifampicin, and ethambutol. One of the secondary cases was his 7-year-old son. Investigation of the 5 identified strains showed that 4 were genetically identical, and 1 patient was therefore removed from this outbreak. Twenty-seven contacts were investigated for that outbreak and 5 cases of latent infection were found.

Outbreak 17, in a family, involved a 29-year-old woman with AIDS. Investigation of contacts revealed that her husband had died 3 months after a diagnosis of tuberculosis and that he also had AIDS. Latent tuberculosis infection was detected in their 2 children, 11 and 4 years old, and they were treated with isoniazid. Two months later, noncavitary pulmonary tuberculosis was found in 1 of the children when new radiographs were taken. He was prescribed a 3-drug antituberculosis treatment.

Outbreak 18 was detected in a psychiatric facility, where a 41-year-old female index case generated 3 secondary cases. The first was a 42-year-old friend who visited often, the second a 22-year-old female inpatient at the facility, and the third a 31-year-old male doctor at the same facility. Among the 170 worker and patient contacts who were investigated, 9 had positive tuberculin skin tests and 55 were infected.

Discussion

There are few publications in the international literature on tuberculosis outbreaks in spite of the vast literature on this old disease. A search of the MEDLINE database between 1984 and 2004 produced only 188 publications with both the key words *outbreak* and *tuberculosis* in the title (9 per year searched). There are also few publications in the Spanish national literature that treat outbreaks in Spain (Table 4). More publications are available, however, on tuberculosis transmission: MEDLINE located 384 published between 1984 and 2004 with both *transmission* and *tuberculosis* in the title.

The 27 outbreaks we analyzed are only the tip of the iceberg, as some ostensibly sporadic tuberculosis cases recorded as part of tuberculosis and general surveillance programs may pertain to the outbreaks. Furthermore, tracing is not done systematically for all outbreaks, as evidenced by the assessment of reports examined in the present study. Geographic variations in outbreaks by health care area would also be attributable to a rate of under notification. We have defined an outbreak by the identification of 3 or more cases. Adoption of a definition of 2 or more related cases,[10] would have increased the number identified considerably. Thus, whereas 9 outbreaks were identified in Barcelona City during 2002 and 2003 according to the 3-case criterion, there would have been 27 outbreaks if the 2-case

TABLE 4
Articles on Tuberculosis Outbreaks in Spain*

Year	Authors	Title	Bibliographic Information	Case	Secondary Cases	Contacts Investigated
2003	Sánchez Marenco A, Borja Pérez C, Rubio Luengo MA, Peinado Garrido A, Sola Fernández C, Castillo Megías M	Brote de tuberculosis en colegio de Granada [Epidemic outbreak of tuberculosis in a primary and secondary school in Granada (Spain)]	An Pediatr (Barc). 2003;58:432-7	1	7	7
2001	Bernaola Iturbe E, Barricarte Gurrea A, Urtiaga Domínguez M, Hernández Lagunas T, Torroba Álvarez L	Brote epidémico de tuberculosis [Epidemic outbreak of tuberculosis]	An Esp Pediatr. 2001;55:25-9.	1	3	61
2000	Perfecto B, Sánchez JR, González AI, López I, Dorronsoro I	Brote de tuberculosis multirresistente [Outbreak of multiresistant tuberculosis]	An Sist Sanit Navar. 2000;23:257-63.	6	NA	NA
1997	Guerrero A, Cobo J, Fortún J, Navas E, Quereda C, Asensio A, et al	Nosocomial transmission of *Mycobacterium bovis* resistant to 11 drugs in people with advanced HIV-1 infection	Lancet. 1997; 350:1738-42	19	NA	NA
1997	Godoy P, Díaz JM, Álvarez P, Madrigal N, Ibarra J, Jiménez M, et al	Brote de tuberculosis: importancia del tiempo de exposición/ proximidad de fuente de infección [Tuberculosis outbreak: significance of exposure time versus proximity to infection source]	Med Clin (Barc). 1997;108:414-8	1	7	30 (A) 31 (B) (2 class room)
1997	Calpe JL, Chiner E, Sánchez E, Armero V, Puigcerver MT, Carbonell C, et al	Microepidemias de tuberculosis 2 brotes escolares, Comunidad de Valencia [Microepidemics of tuberculosis; apropos of 2 school outbreaks in the area 15 of the Valencia community]	Arch Bronconeumol. 1997;33:566-71	1 (A) 1 (B)	13 (A) 2 (B)	616 (A) 175 (B)
1997	Vidal R, Miravitlles M, Caylá JA, Torrella M, de Gracia J, Morrell F	Incresed risk of tuberculosis transmission in families with microepidemics	Eur Respir J. 1997;10:1327-31	176	NA	3071
1993	Querol JM, Oltra C, Granda D, Alonso MC, Climent JL, Labrador T, et al	Descripción de una microepidemia escolar de tuberculosis [Description of a school micro-epidemic of tuberculosis]	Enferm Infecc Microbiol Clin. 1993;11:267-70	1	8	59
1991	Cabáñez Argudo M, Sánchez García S, Franco Serrano J	Brote familiar de tuberculosis respiratoria [Familial outbreak of pulmonary tuberculosis]	An Med Interna. 1991;8:291-3	1	4	7
1990	Vidal R, Roca R, Miravitlles M, de Gracia J, Nubiola AR	Microepidemia familiar de tuberculosis [Familial microepidemics of tuberculosis]	Med Clin (Barc). 1990;95:221-3	1	4	12
1989	Boqué MA, de March Ayuela	Microepidemias escolares de tuberculosis; 13 casos de tuberculosis en Barcelona [Tuberculosis microepidemics in schools. Apropos of 13 cases detected in Barcelona]	An Esp Pediatr. 1989;30:261-4	13	NA	688
1988	de March Ayuela P, Boqué Geovard MA	Brotes explosivos: 10 epidemias escolares en Barcelona [Sudden outbreaks of tuberculosis: apropos of 10 school epidemics in Barcelona and its province]	Rev Clin Esp. 1988;183:24-9	1	53	1268

*NA indicates not available.

definition had been used.[18] Outbreaks of 3 or more cases represented an outbreak incidence rate of 0.19/100 000 inhabitants in the 2-year period of 2002 and 2003. If the same rate held over 5 years, the outbreak incidence rate would be 0.5/100 000 inhabitants—much higher than the incidence we actually found.

Our report shows that most outbreaks take place within families and are generated by males aged 16 to 40 years with cavitary lesions. Diagnostic delay is considerable in most cases, as others have pointed out.[19-21] The mean (SD) diagnostic delay of 72.64 (43.86) days is also noteworthy as it is longer than delays reported by other authors of 36 to 58 days,[4,22,23] although some groups have also detected long delays.[24,25] Likewise, we saw a tendency to linear correlation between the number of secondary cases and the length of diagnostic delay, although the *P* value was .08, probably because of lack of statistical power. There was also a certain dose-response relation in the comparison between the category of delay of fewer than 35 days and the other 2 categories, in the sense that the number of secondary cases detected increased with days.

HIV infection is known to favor the development of tuberculosis disease from either endogenous reactivation or exogenous reinfection.[26] Therefore, this virus played an important role in some of the outbreaks, a finding consistent with reports of tuberculosis in HIV-infected individuals,[27] including cases of infection by multidrug-resistant *Mycobacterium bovis*.[28]

Immigrants, like other disadvantaged social groups, are the most vulnerable to tuberculosis because of overcrowded living conditions and the high prevalence of the disease in their countries of origin, among other factors.[29,30] The involvement of the immigrant population in the outbreaks we analyzed was limited, however, although other reports in Spain have seen a clear relationship,[31] including the introduction of highly virulent strains.[32]

The true index cases can differ from the initial index cases that led to investigation, at a rate of nearly 20% as seen in the present study, and some outbreaks require extended tracing to locate the true index case. It is therefore important to continue tracing until the real source of infection for an outbreak is found. Maximum coordination between conventional contact tracing and new methods of molecular epidemiology can therefore be highly useful in locating the source.[33-35] Contact tracing should start as soon as possible to take advantage of the impact a diagnosis of tuberculosis will have on the patient and his or her contacts,[17] with the aim of early detection of other tuberculosis cases or even of their prevention. However, it is considered that these new techniques should not be promoted in the community until conventional contact tracing has demonstrated its utility, as it is quite common for the tuberculosis surveillance programs of different Spanish autonomous communities not to have reliable or adequate data for tracing contacts.[36] Conventional contact tracing is a priority whenever a tuberculosis case is identified in order to find true index cases as well as secondary cases and infected individuals.

Molecular epidemiology techniques currently allow us to study the geographic distribution of *Mycobacterium tuberculosis* clones, to confirm or rule out outbreaks, to detect outbreaks that mimic sporadic cases of tuberculosis, to detect recent or rapidly progressing ones, to study transmission patterns that point to population groups that should receive priority attention from surveillance programs, to rule out cross contamination in the laboratory,[35,37,38] and to evaluate the effectiveness of contact tracing itself.[39] The most useful technique is restriction fragment length polymorphism, which allows the genetic patterns of thousands of strains to be entered into databases for the detection of associated cases. Molecular strain typing of *M tuberculosis* also allows reactivation of a strain to be distinguished from reinfection by another one. Genetic fingerprinting of multidrug-resistant strains is especially important given their high economic and social costs, as control measures can thereby be established to prevent transmission of such strains on both international and national levels.

Finally, we recommend that, at least in developed countries, surveillance or control programs should issue appropriate reports so as to monitor the situation and provide a better understanding of tuberculosis transmission, thus enabling better prevention and control of this old disease.

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