ABSTRACT

The evidence regarding the transmission of tuberculosis and risk of infection and disease in several specific clinical situations has been reviewed. There is considerable epidemiologic evidence that contagiousness is not an all-or-nothing phenomenon and is affected by several factors, only one of which is the bacteriologic status of the patient's sputum. Although untreated smear negative, culture positive patients are less contagious on average, they still may transmit infection to their close and casual contacts. Compared with contacts with tuberculin conversion, persons who are already tuberculin positive have much lower risk of developing active tuberculosis after exposure, and persons with prior BCG vaccination are at somewhat lower risk. Preventive therapy will be of less benefit, but should still be recommended for contacts who are heavily exposed or are immune compromised. Epidemiologic studies using RFLP techniques could provide more precise answers to the questions in this review.

ABRÉGÉ

On a passé en revue les données concernant la transmission de la tuberculose et le risque d'infection et de maladie dans plusieurs situations cliniques particulières. Il existe un nombre considérable de données épidémiologiques montrant que la contagion n'est pas un phénomène clair et net et qu'elle est influencée par plusieurs facteurs, l'état bactériologique des expectorations n'en constituant qu'un parmi d'autres. Bien que (de frottis d'expectorations négatif) les patients positifs à la coproculture soient moins contagieux en moyenne, ils restent susceptibles de transmettre l'infection à leurs proches et à ceux avec lesquels ils ont de simples contacts. En comparaison avec les sujets contacts avec conversion tuberculinique, les personnes qui réagissent déjà positivement à la tuberculine ont un nettement moins grand risque de développer une tuberculose évolutive après exposition, et les personnes vaccinées au BCG ont moins de risques également. Bien qu'offrant moins d'avantages, une thérapie préventive doit tout de même être recommandée aux sujets contacts très exposés ou à ceux dont l'immunité est déprimée. Les études épidémiologiques se servant des techniques du polymorphisme des sites de restriction pourraient permettre d'obtenir des réponses plus précises aux questions soulevées dans cet article.

Issues in the Management of Contacts of Patients with Active Pulmonary Tuberculosis

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The challenges posed by the recent resurgence of tuberculosis,[1,2] the emergence of multidrug resistant strains,[3-5] and the HIV epidemic have prompted a critical reappraisal of many traditional tuberculosis control practices in North America. There is considerable debate regarding the contagiousness of patients with smear negative, culture positive pulmonary TB, or patients who are smear negative on spontaneous sputum but smear positive on induced sputum or bronchoscopic lavage specimens. The need for preventive therapy for contacts who are already tuberculin positive or who have been BCG vaccinated and re-exposed is also controversial.

The available epidemiologic and experimental information has been reviewed to clarify these issues and to identify where further information is needed.

METHODS

To identify relevant articles for this review, the Medline database was searched from 1965 to 1996 using the following keywords: pulmonary tuberculosis, transmission, public health practices, contact tracing, infection control, and nosocomial transmission. These terms were cross-indexed with gastric lavage, induced sputum, and bronchoscopy to address the specific question of the interpretation of these results. All relevant articles identified from the search were reviewed. The references cited in these articles were used to identify additional relevant material. The protective efficacy of BCG vaccine was not reviewed; rather, the results of a recent meta-analysis[6] were used.

The evidence given in this review was taken from four types of studies: a) in-vitro laboratory studies, b) experimental studies with animal models of the factors affecting transmission; c) outbreak reports providing information on factors associated with transmission; and d) epidemiologic population-based studies that provided sufficient information for risk of infection or disease to be estimated for different risk factors, such as bacillary status of the index cases or type of contact.

RESULTS

How contagious are patients with smear negative yet culture positive pulmonary TB, i.e., Do their contacts need to be examined?

Apart from technical factors,[7] the likelihood that a sputum specimen will be classified as smear negative or positive depends on the bacillary concentration in the sputum. When the bacillary concentration exceeds 10^5 per mL, acid fast bacilli (AFB) will almost invariably be seen on direct microscopy; at 10^4 per mL the likelihood of seeing a single AFB on examination of 100 high power fields is only 50%.[7-9] The critical concentration to detect any AFB on smear is between 5,000 and 7,800 bacilli per mL.[8-11]

Patients with active respiratory tuberculosis generate aerosols of droplets containing viable tubercle bacilli when they cough, talk or sneeze.[12] It has been shown that inhalation by guinea pigs of a single droplet containing as few as 1-3 viable tubercle bacilli will reach the level of the pulmonary alveolus[13] and result in infec-

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Supported by the Fonds de Recherche en Santé du Québec

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TABLE I
Risk of Infection Among Household (Close) Contacts According to Bacteriologic Status of Index Case (Pulmonary TB Only)

Ref No.	Year of Survey	Location	Contacts Age	Contacts Total No.	Number and % Infected Contacts by Bacteriologic Status of Index Case S^+C^+ N	S^+C^+ %+	S^-C^+ N	S^-C^+ %+	S^-C^- N	S^-C^- %+	General Population % positive PPD*
28	1949-56	England	0-14	545	262	63%	126	21%	157	18%	13%
29	1950-53	England	0-14	823	374	65%	228	27%	221	18%	22%
11	1963-64	Holland	all ages	858 †	391	20%	467	1%	—	—	<<1%
30	1966-71	Canada-Whites	0-19	2406	1210	38%	655	12%	541	10%	2%
		Canada-Aboriginals	0-19	1168	592	45%	377	31%	199	27%	NA
31	1967-69	Rotterdam	0-14	134	40	50%	43	5%	51	8%	1%
12	1969	USA	all ages	130	88	44%	14	21%	28	14%	NA
27	1971-74	USA	all ages	761	504	46%	257	28%	—	—	NA
19	1975-77	USA	all ages	541	368	40%	173	27%	—	—	NA

* Taken from same reference, i.e., a comparable reference population.
† In this study contacts considered infected only if tuberculin conversion and/or primary TB documented.

TABLE II
Incidence of Disease Among Household (Close) Contacts According to Bacteriologic Status of Index Case (Pulmonary TB Only)

Ref No.	Year of Survey	Location	Length of follow-up	Incidence of Disease Among Contacts by Bacteriologic Status of Index Cases S^+C^+ Total N	S^+C^+ Incid N	S^+C^+ Disease %	S^-C^+ Total N	S^-C^+ Incid N	S^-C^+ Disease %	S^-C^- Total N	S^-C^- Incid N	S^-C^- Disease %	General Population Incidence (%)*
29	1950-54	England	1-2 yrs	374	48	13%	228	6	3%	221	2	1%	0.06%
32	1960-61	Ontario	6 mos	539	35	7%	396	5	1%	181	2	1%	0.03%
30	1966-71	Canada-Whites	6 mos	1088	123	11%	578	10	2%	464	3	1%	0.03%
		Canada-Aboriginals	6 mos	707	85	12%	396	11	3%	192	4	2%	0.04%
33	1977-81	Edinburgh	6 mos	240	25	10%	209	6	3%	621	8	1%	0.03%
Total				**2948**	**316**	**10.7%**	**1807**	**38**	**2.1%**	**1679**	**19**	**1.1%**	

* Annual incidence expressed in %: 0.03 = 30/100,000.

tion, manifested as tuberculin conversion and formation of granulomas.[14] The probability of inhaling a single droplet containing TB bacilli will be determined by the duration of exposure, rate of removal by ventilation or inactivation, and the rate of generation from infectious patients.[15,16]

Patients with positive AFB smears have higher concentrations of bacilli in their sputum, so are more likely to generate air-borne droplets containing TB bacilli.[7,11] Patients who are smear negative but culture positive (S^-C^+) should have fewer bacilli,[7,11] and so generate fewer infectious particles. However, it seems improbable that they would generate none at all, and the reduced bacillary concentration of their sputum may be offset by other factors, such as laryngeal involvement,[17,18] younger age[12,19] or more frequent cough.[12,20-23] Therefore, a young S^-C^+ patient with frequent cough could be more contagious than an elderly smear positive, culture positive (S^+C^+) patient who coughs rarely. In addition, transmission may be enhanced by crowding,[24,25] low air exchange rates[24,26] or longer duration of contact.[17,25,27]

Table I summarizes the epidemiologic studies on the risk of infection in household (close) contacts grouped according to the bacteriologic status of the index cases. In general, the prevalence of significant tuberculin reactions among household contacts was highest for contacts of S^+C^+ cases, intermediate for contacts of S^-C^+ cases and lowest for contacts of smear negative, culture negative (S^-C^-) cases. The prevalence of infection in the general population, measured in the same studies, was substantially lower.

As summarized in Table II, the incidence of disease was consistently highest among household (close) contacts of S^+C^+ patients. The incidence of disease among household contacts of S^-C^+ patients was higher than among contacts of S^-C^- patients, and both were much higher than among the general population.

In these same studies the incidence of disease or prevalence of infection was 4 to 10 times higher among close/household contacts than among casual/non-household contacts of the same cases (data not shown in Table II).[27,30,31,33] Among casual/non-household contacts the occurrence of infection and disease was consistently more frequent among contacts of S^+C^+ cases than of S^-C^+ cases. A few larger studies have detected excess occurrence of infection and disease among casual/non-household contacts of S^-C^+ patients, compared with the general population. The effect detected was small, which explains why smaller studies had insufficient power to detect significant transmission to casual contacts from S^-C^+ cases.

In one study, the incidence of tuberculosis within six months was calculated for tuberculin positive contacts who were less than 20 years old.[30] Among household (close) contacts who were PPD positive on tuberculin skin testing, disease developed in 6.5% of those who had had contact with S^+C^+ cases, compared with 1.8% of those exposed to S^-C^+ cases (relative risk 3.6). In the same survey, among PPD positive casual contacts active tuberculosis developed within six months in 3% of those exposed to S^+C^+

TABLE III
Evidence for Relative Protection of Prior Infection

Ref No.	Year of Survey	Location	Population/ exposure	Age when exposed	Length of follow-up	Pre-exposure tuberculin status	Tuberculin positive* N	Developed Active TB N	Developed Active TB %	Protective Effect
46	1924-26	Oslo	Nursing students	18-21	3 yrs	Negative	284	97 †	34%	—
						Positive	668	22	3.3%	90%
47	1932-48	Boston	Nursing students	18-21	5-15 yrs	Negative	285	38	13.6%	—
						Positive	374	31	8.3%	39%
48	1934-43	London	Nurses	18-24	3 yrs	Negative	427	33	7.7%	—
						Positive	2120	43	2.0%	74%
49	1934-49	Baltimore	Medical students	19-24	4 yrs	Negative	319	11	3.4%	—
						Positive	747	5	0.7%	79%
			Nursing students	18-21	3 yrs	Negative	163	7	4.3%	—
						Positive	258	1	0.4%	91%
30	1966-71	Saskatchewan & B.C.	General pop'n	0-14	6 mos	Negative‡	692	82	12%	—
			Close contact	30+		Positive‡	1064	29	3%	75%
			General pop'n	0-14	6 mos	Negative‡	360	24	7%	—
			Close contact	30+		Positive‡	1494	20	1.3%	81%
50	1992	Arkansas	HCW/outbreak	NA	3 mos	Negative	36	5	14%	—
						Positive	10	0	0	infinite

* For those initially negative only the number with conversion shown.
† Of these 12 (4.2%) died of active TB.
‡ Assumed tuberculin status based on prevalence in general population of same age.

index cases, compared with 1.2% of those exposed to S^-C^+ cases (relative risk 2.5). In the same years, the prevalence of infection in the general population of the same age was 2%, and the annual incidence of disease averaged 11 per 100,000, i.e., active TB developed in 0.27% of tuberculin reactors in the general population each year. On the basis of these figures, it can be estimated that the incidence of active TB among PPD positive casual contacts of S^-C^+ cases was 4.8 times higher than for PPD positive persons of the same age in the general population.[30]

How contagious are patients who are sputum smear negative but smear positive on induced sputum, bronchoscopic lavage or gastric lavage?

For patients who have no sputum or are smear negative on examination of spontaneous sputum, gastric aspirates,[34-36] sputum induction[37-41] and fibreoptic bronchoscopy[37,42-44] are increasingly used, because they have a high yield and allow earlier diagnosis of tuberculosis. Although most patients whose TB is diagnosed with these alternative methods have shown minimal or moderately advanced disease on radiographic examination,[34,36,44,45] some series reported that as many as one-third had far-advanced[35,41] or cavitary[37] disease, and between 22% and 35% of specimens from these alternative techniques were smear positive.[34,37,42-44] Therefore, the question of the contagiousness of such patients arises frequently but, to date, has not been studied directly. In the absence of any solid epidemiologic information, it would be prudent to consider the results of these alternative diagnostic methods as equivalent to the results from spontaneous sputum.

Should preventive therapy be given to a contact who is already PPD positive (and has never received BCG vaccine) following exposure?

Studies using restriction-fragment-length polymorphism (RFLP) techniques have demonstrated that in outbreak situations re-infection can occur and result in active disease. Absolute and relative risks can be estimated from a number of cohort studies, summarized in Table III. In the pre-antibiotic era, nurses or students in nursing or medicine were tuberculin tested before beginning clinical work, and re-tested annually or at graduation.[46-49] Exposure to TB was very common, and 50 to 80% of the initially uninfected converted each year, meaning that almost everyone became infected within three to four years.[46-49] During two to four years of follow-up, the incidence of disease was very high among those with tuberculin conversion but 80% lower among those initially tuberculin positive. If exposure occurred independently of baseline tuberculin status, then being tuberculin positive before exposure provided a protective effect of approximately 80%.[46-49] From rates of age-specific prevalence of infection and incidence of disease in the Netherlands, Sutherland[51] calculated that remote primary infection reduced by 79% the likelihood of active pulmonary TB developing after re-infection — a remarkably similar estimate.

A similar phenomenon was observed among PPD positive contacts of confirmed cases of active TB diagnosed in Saskatchewan and British Columbia between 1965 and 1971. Contacts who were aged 0 to 14 were assumed to have been tuberculin negative, and contacts aged 30 or older to have been tuberculin positive, prior to exposure. As shown in Table III, the incidence of culture confirmed disease within six months among the older contacts was only 25% of the rate among younger contacts.[30] Recently, disease developed in 5 of 36 health care work-

ers with documented tuberculin conversion compared with 0 of 10 who were known to be tuberculin positive and had had similar exposure.[50]

Should preventive therapy be given to a contact who is already PPD positive and has received BCG vaccine?

This corollary question has not been addressed directly in studies of exposed populations. It is well known that tuberculin reactivity can persist for many years in a substantial proportion of persons vaccinated after infancy.[52] A recent meta-analysis[6] concluded that BCG provided 50 to 60% protection from active disease, i.e., less than natural infection. Using the logic described in the previous section, a known reactor attributed in the past to BCG vaccination should be considered at some risk of disease after significant exposure. Preventive therapy should still be considered, particularly in the circumstance of close contact, immune compromise or other risk factor.

FUTURE STUDIES

Current concepts regarding transmission and contact investigation are based on the tuberculin skin test, a technique first introduced at the turn of the century. Tuberculin testing cannot distinguish new from old infection, a major limitation in populations with a high prevalence of tuberculosis infection. As well, false negative tests are common among elderly[53] or immunocompromised[54,55] patients, and false positive tests are common among populations who are foreign-born,[56] BCG vaccinated[52,57] or are sensitized to non-tuberculous mycobacteria[58,59] — the population groups most at risk in North America.

A new technology, RFLP, allows precise identification of individual strains of microorganisms. RFLP has been used in outbreak situations to establish who is affected, and the modes, locations and patterns of transmission.[60-62] Recent community-based studies using RFLP have detected significant transmission, not recognized by standard contact tracing, under circumstances in which exposure was limited and transmission would not have been anticipated according to traditional public health concepts.[63-65] RFLP could be of use in studying modern transmission of tuberculosis, for example by delineating factors affecting the contagiousness of S^-C^+ patients and the transmission of TB from such patients, or by detecting environments in the community where transmission occurs.

CONCLUSIONS

1. All the experimental and epidemiologic evidence suggests that contagiousness is a continuous rather than an all-or-nothing phenomenon. Transmission is affected by several factors, only one of which is the bacteriologic status of the patient's sputum. Although S^-C^+ patients are less contagious on average this can be offset by other factors, including more frequent cough, younger age, prolonged contact, or low rate of removal of airborne infectious particles. Therefore, untreated smear negative, culture positive patients should be considered contagious, and their contacts investigated.
2. In assessing the contagiousness of patients, the microbiologic results obtained from gastric aspirates, bronchial lavage, or induced sputum should be considered equivalent to those of spontaneous sputum.
3. The epidemiologic evidence consistently shows that after exposure, persons who are tuberculin positive on the basis of prior tuberculous infection are at much lower risk for the development of active TB than contacts who are tuberculin negative and become newly infected. Accordingly, the benefit of preventive therapy will be less, but should still be recommended for contacts who are heavily exposed or are immune compromised.
4. After exposure, persons who are tuberculin positive on the basis of prior BCG vaccination are at somewhat lower risk for the development of active TB. Preventive therapy should be recommended for persons who are close contacts or have other risk factors.
5. Epidemiologic studies using RFLP techniques could provide more precise answers to these questions.

ACKNOWLEDGEMENTS

The author acknowledges the financial support provided by the Fonds de Recherche en Santé de Quebec and the critical review provided by Dr. Kevin Schwartzman.

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Received: March 28, 1996
Accepted: January 24, 1997