

Isoniazid resistant tuberculosis in a school outbreak: the protective effect of BCG

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Isoniazid resistant tuberculosis in a school outbreak: the protective effect of BCG. A. Shannon, P. Kelly, M. Lucey, M. Cooney, P. Corcoran, L. Clancy.

ABSTRACT: An outbreak of isoniazid resistant tuberculosis occurred in a large second level school. A total of 1,160 teenage pupils were at risk. Nineteen cases of tuberculosis were diagnosed, 15 were students, 9 of whom were among 251 non-vaccinated students and 6 among 909 vaccinated students. Two cases of miliary tuberculosis, one of whom also had tuberculous (TB) meningitis, occurred in the non-vaccinated group. The number of children with Heaf grade +3 or +4 was significantly greater among children who had been given Bacille Calmette-Guérin (BCG) vaccination (8 vs 4.4%). This suggests a boosting effect on the response in vaccinated children. The protective effect of neonatal BCG vaccination in this school outbreak suggests that it provides significant protection against tuberculosis lasting into adolescence.

Eur Respir J, 1991, 4, 778-782.

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Keywords: Bacille Calmette-Guérin (BCG); isoniazid resistance; mini-epidemic; school outbreak; tuberculosis.

Received: October 24, 1989; accepted after revision December 13, 1990.

Localized outbreaks or mini-epidemics of tuberculosis are well described [1-7]. In this study we describe a mini-epidemic of tuberculosis occurring in a large second level school. It is of note that the organism was found to be isoniazid resistant. A large number of teenage children were involved and it allowed a unique opportunity to compare the outcome in Bacille Calmette-Guérin (BCG) vaccinated and non-vaccinated children.

The school

The school involved is a large second level school (day pupils only) of 1,138 pupils aged 12-18 yrs. It services a large area of north east Donegal in the north west part of the Republic of Ireland. The community is largely agricultural/fishing and mainly rural. The children travel by bus into school in the town from outlying districts. While the policy in the Community Care Area is to give neonatal BCG vaccination, many children at the school were born outside the area or were the children of returned emigrants and had not received BCG vaccination.

Index cases

Between late February and early April, 1986, three teenage girls at the school were diagnosed as having tuberculosis.

Case 1: Aged 17 yrs. History of neonatal BCG vaccination; pleural effusion from which tubercle bacilli were cultured.

Case 2: Aged 19 yrs. History of neonatal BCG vaccination. Large right-sided pleural effusion. Pleural biopsy was positive for tuberculosis.

Case 3: Aged 14 yrs. No BCG vaccination. Miliary tuberculosis and tuberculous meningitis. Cerebrospinal fluid was positive on culture for tuberculosis.

The three index cases all had a positive response (greater than 10 mm) to 1 tuberculin unit (TU) Mantoux. All three girls presented to their family doctors.

Population and methods

All pupils, teachers and ancillary staff at the school were screened. A record was made of each person's BCG vaccination history and whether scars were present, and personal or family history of tuberculosis. Basic personal data was available from the school computer files. BCG vaccination records were available from the Public Health Department.

In addition to the above, the families and home contacts of children and staff diagnosed as having tuberculosis were screened, as were staff in recreational areas, e.g. local cafes, shops, transport, facilities frequented by the students.

All persons screened had a Heaf test and chest X-ray. The Heaf test was used in preference to the Mantoux

Table 1. — The Heaf test results for 1,160 children attending the school, (including 25 children who had recently left school) for the first screening test

	n	Neg.	+1	+2	+3	+4
BCG	909	312 (34%)	217 (24%)	308 (34%)	62 (7%)	10 (1%)
No BCG	251	205 (82%)	10 (4%)	25 (10%)	6 (2.3%)	5 (2%)

Those regarded as having had BCG vaccination had a record of vaccination or BCG scars present or both. BCG: Bacille Calmette-Guérin.

Table 2. — Details of patients

Case no.	Age yrs	Sex	Date of diagnosis	BCG vaccination	Tuberculin test	Clinical	Bact./Hist.
1*	17	F	22/2/86	Yes	Mantoux 1 TU+ve	Pleural effusion	C+ (fluid)
2*	19	F	13/3/86	Yes	1 TU+ve	Pleural effusion	Bx positive
3*	14	F	03/4/86	No	1 TU+ve Heaf	Miliary & meningitis	S+, C+, CSF+
4†	17	F	23/4/86	No	+3	Pulmonary LMZ lesion	Negative
5	16	F	25/4/86	No	+4	Pulmonary - miliary	C+
6	16	M	25/4/86	No	+4	Consolidation RLL	Negative
7	18	F	02/5/86	Yes	+4	Lesion right apex	C+
8†	14	F	02/5/86	No	+2	Opacity & cavity RMZ	Negative
9	17	M	02/5/86	No	+4	RLL consolidation	C+
10	15	F	02/5/86	No	+2	Opacity & cavity LMZ	S+, C+
11†	18	F	16/5/86	No	+3	R. pleural effusion	Negative
12	13	M	23/5/86	No	+2	Opacity right apex	C+
13†	19	F	30/5/86	Yes	Neg.	Small opacity R. apex	Negative
14	16	M	11/7/86	Yes	+3	Pleural effusion	Negative
15†	17	M	06/5/87	Yes	+2	Pleural effusion	C+ (fluid)
Non-students							
16*	29	M	23/4/86	No	+2	Opacity left apex	S+, C+
17†	28	M	06/6/86	No	+2	Opacity right apex	Negative
18	2	M	31/7/86	No	+3	RML collapse	Negative
19†	2	M	15/11/86	No	+3	Consolidation RMZ	Negative

Bact./Hist.: Bacteriological/Histological status; *: initial three cases; †: diagnosis made on clinical/radiological grounds; ‡: teacher; S+: smear positive; C+: culture positive; Bx: biopsy positive; CSF+: cerebrospinal fluid positive; RLL: right lower lobe; RML: right middle lobe; RMZ: right middle zone; LMZ: left middle zone.

test as it was considered easier to administer to a large group. The test was read in a standard manner as recommended [8]. Those with abnormal chest X-rays or symptoms were assessed for active disease.

As the screening programme evolved, and because the pupils came from a wide geographical area and many had siblings attending primary school, all children in the local primary schools were Heaf tested. Social contacts and contacts in other second level schools of children with tuberculosis were also screened. Open access, walk-in clinics were also operated.

Two months after the initial screening all pupils who had been negative on the initial test were Heaf tested again and chest X-rays repeated on high risk individuals. Those with negative response to the second Heaf test

were offered BCG vaccination. Screening was on a voluntary basis. The Chi² test was used in all comparisons.

Results

All 1,135 students (excluding the three index cases) attending the school were screened as were 25 of 30 children who had recently left school (1,160 students). Results of their Heaf tests and BCG status are given in table 1. The degree of positivity by Heaf testing (Heaf grade +3 and Heaf grade +4) was statistically significantly more positive in those children who had been vaccinated ($p=0.001$).

Table 2 shows details of all 19 persons who had a diagnosis of TB and the date of diagnosis is indicated on the table. The 3 index cases and cases number 15 and 18 presented with symptoms. The remaining cases, including what may have been the source case, were detected by screening. In all, 15 students - 6 in the BCG vaccinated group (including two of the index cases) and 9 who had not received vaccination, had tuberculosis. and another with miliary tuberculosis and tuberculous meningitis. The difference in incidence of tuberculosis between children who had been vaccinated and the non-vaccinated children was statistically significant ($p=0.001$; $\chi^2=10.997$; $DF=1$). The relative risk of non-vaccinated children getting tuberculosis as compared to vaccinated children was 5.43 (95% confidence interval (CI); 1.95-15.1). Two hundred and ten children had received vaccination in primary school. None of these children had active tuberculosis. Analysis comparing those who had only had neonatal BCG with those who never had BCG also shows a protective effect of the BCG vaccine which was statistically significant ($p=0.004$).

The possibility that stratified behaviour within the school, social outlets in the school, or in general social outlets or transport might have been responsible for a different level of exposure for students who had BCG and those who had not was investigated but no bias in terms of exposure could be demonstrated.

Seventy eight teachers were screened. Two teachers (Cases 16 and 17) had active pulmonary tuberculosis, one being sputum positive at the initial screening and the other diagnosed at the two month follow-up examination. Three other teachers had evidence of old inactive tuberculosis. Forty two ancillary school staff were screened and four had evidence of previous primary infection. None had active disease.

Of 331 family contacts screened, 2 were given chemoprophylaxis and 6 others had evidence of old inactive lesions. A 2 yr old boy who was not screened in the initial contact tracing was subsequently diagnosed as tuberculous (Case 18). Another 16 yr old boy (Case 14), who had neonatal vaccination but who had left school prior to screening, presented to his family doctor with a tuberculous pleural effusion. One 19 yr old pupil (Case 13) had tuberculosis but a negative skin test. She had recently recovered from an episode of chickenpox and it was felt that this may have been responsible for the initial negative skin reaction. A further 30 children who had recently left secondary school were also identified and 25 of these attended for screening. None had evidence of tuberculosis.

Publicly advertised open clinics were held in the two main towns. A 2 yr old boy (no previous BCG) had a +3 Heaf result and a right middle lobe consolidation radiologically (Case 19). No definite contact could be established with the school and he was not bacteriologically proven as tuberculous. He responded to therapy. No tuberculosis was found in any of his contacts. For completeness he is included in this study but he may not have been part of the outbreak.

The second screening of the students at the school and the screening of the primary school contacts yielded no further cases of tuberculosis.

All isolates were identified as *Mycobacterium tuberculosis* and all were strongly resistant to isoniazid. All cases of tuberculosis were treated with a three drug regimen of rifampicin, isoniazid and ethambutol for a minimum duration of twelve months. Treatment for miliary tuberculosis and TB meningitis was more prolonged. Children who had a +3 or +4 Heaf without previous BCG vaccination and children with a +4 Heaf with previous BCG vaccination were given chemoprophylaxis. Initially chemoprophylaxis had been started with isoniazid alone but when the isolates were identified as isoniazid resistant chemoprophylaxis was changed to rifampicin and ethambutol for a six month period.

Dealing with non-medical aspects of the epidemic

Tuberculosis causes anxiety and is often associated in the minds of the public with chronic ill health and death. Because of the number of children involved in the screening process and the number of cases diagnosed, public anxiety needed to be allayed. The school principal and school authorities were instrumental in keeping parents informed of developments. All patients were circulated with a letter informing them that an outbreak of tuberculosis had occurred and requesting consent for Heaf testing and screening of each child. They were also given an information sheet giving an outline of tuberculosis, its cause and methods of transmission and reassuring them that it was treatable and curable. Meetings were held with the teaching staff to explain the situation, the diagnosis and the measures which had to be taken.

Where there was a chest X-ray abnormality or a suspicion of active disease the patients and family were met by one of us and the findings and diagnosis discussed. Each general practitioner in the area was informed by letter of the problem and the steps being taken in contact tracing and their co-operation was enlisted in allaying anxiety.

The Medical Officer of Health met with the general practitioners in the area, the teachers staff association and the parents of the school children to detail the epidemic, the screening measures necessary and to allay their fears. This co-operation together with the assistance of the Departments of Radiology, the physicians and paediatricians in Letterkenny General Hospital was an important factor in dealing with the epidemic.

The media

As could be anticipated with a significant outbreak the national and local media picked up the story and it was carried in national newspapers and television. Initial response was somewhat sensational which contributed to

parental and community concern. The Medical Officer of Health was interviewed by national television and the school principal by one of the national newspapers.

Discussion

This mini-epidemic of tuberculosis offered a unique opportunity for assessing the benefits of previous BCG vaccination among a large group of teenage students exposed to TB. The protective effect of BCG vaccination has been demonstrated for young children [9, 10] but whether neonatal BCG protection lasts to adolescence is unclear. In this mini-epidemic good protection is suggested by the different rates of tuberculosis in the two groups of students which was statistically significant. BCG vaccination either in the neonatal period or during primary school gave a high degree of protection against tuberculosis in this outbreak.

There is debate about the future of BCG vaccination in Ireland, particularly its administration in the neonatal period as a uniform policy. The argument is that BCG vaccination may not be necessary in a country where tuberculosis is declining and that mass BCG vaccination decreases the value of the tuberculin test in screening contacts in outbreaks of tuberculosis. The counter argument is that, as in this mini-epidemic, BCG does afford protection against tuberculosis, even among teenagers, who were vaccinated as neonates. One of the major problems with the approach to BCG vaccination in Ireland is a lack of uniformity in its application [11]. The argument in favour of neonatal BCG vaccination is the protection believed to be afforded against miliary tuberculosis and TB meningitis in pre-school children in an area of relatively high incidence of tuberculosis. In countries with lower incidence of TB, BCG vaccination preceded by skin testing is advocated at the end of primary school (12-14 yrs) [9], particularly among high risk groups, because of the known susceptibility of tuberculosis for young adults, particularly females [12].

Of note is the tuberculin skin test status of children who had received BCG wherein 8% had a +3 or +4 Heaf in comparison to children without BCG (4.5%). A previous post vaccine Heaf result was available on 50% of vaccinated children, and at that time only one had a +3 reaction. The remainder were either +1 or +2. This suggests a boosting effect of exposure to TB on the skin test response and raises questions about the appropriate action to be taken with regard to chemotherapy in this group. We have also seen this boosting effect in health care workers and the same mechanism may be involved [13].

The infecting strain of tubercle bacillus was isoniazid resistant and this complicated both treatment regimens and chemoprophylaxis. All children have completed treatment without any problems of drug toxicity and without any visual disturbances secondary to ethambutol. All bacteriologically converted to negative and none has relapsed to date. We felt that a 12 month treatment course with rifampicin and ethambutol would be effective.

LEES and co-workers [14-16] have shown that rifampicin and isoniazid for two months followed by isoniazid and ethambutol to a total of 12 months was effective in treating pulmonary tuberculosis. Rifampicin is probably a superior single agent and has a special role in reducing the total duration of treatment and hence our treatment schedule should be adequate.

All the treated patients were followed up for three years and there have not been any relapses nor have any new cases of tuberculosis arisen in the screened untreated group. This is of particular interest with regard to the BCG vaccinated Heaf positive grade III pupils who were not given chemoprophylaxis.

Acknowledgements: The authors would like to acknowledge the help and assistance of the following: M. Boyle, North Western Health Board and the clerical and nursing staff, community clinics, North Western Health Board. Drs C. Mac A'Bhaird and M. O'Carroll and their staff, Department of Radiology; Drs L. Bannan, B. Callaghan, C. Ryan and S. McGuire, Letterkenny General Hospital; Dr F. Kenny, General Hospital Sligo. They would also like to acknowledge the assistance of Dr T. Healy and the microbiology staff, Peamount Hospital, Dublin.

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Tuberculose résistante à l'isoniazide dans une épidémie scolaire: effet protecteur du BCG. A. Shannon, P. Kelly, M. Lucey, M. Cooney, P. Corcoran, L. Clancy.

RÉSUMÉ: L'on a observé une épidémie de tuberculose résistante à l'isoniazide dans une grande école de niveau secondaire. La population soumise à risque était de 1,160

élèves "teenagers". L'on a diagnostiqué 19 cas de tuberculose, dont 15 étaient des étudiants, parmi lesquels 9 se retrouvaient parmi les 251 étudiants non vaccinés et 6 parmi les 909 étudiants vaccinés. Deux cas de tuberculose miliaire, dont un associé à une méningite tuberculeuse, sont survenus dans le groupe non vacciné. Le nombre d'enfants ayant des tests de Heaf de niveau +3 ou +4, est significativement plus élevé chez les enfants vaccinés par le BCG (8 vs 4.4%). Ceci suggère un boosting effect sur la réponse chez les enfants vaccinés. L'effet protecteur d'une vaccination néo-natale au BCG dans cette épidémie scolaire suggère qu'elle assure une protection significative contre la tuberculose jusqu'à l'adolescence.

Eur Respir J, 1991, 4, 778-782.