

Neonatal BCG vaccination in Ireland: evidence of its efficacy in the prevention of childhood tuberculosis

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Neonatal BCG vaccination in Ireland: evidence of its efficacy in the prevention of childhood tuberculosis. P. Kelly, D. McKeown, L. Clancy. ©ERS Journals Ltd 1997.

ABSTRACT: Data from the 1986 and 1991 National Tuberculosis Survey were used, together with the Census of Population for those years, to try and determine whether bacille Calmette-Guérin (BCG) vaccination policy had any influence on the reported incidence of tuberculosis in the Republic of Ireland.

The age-specific incidence of tuberculosis for the country as a whole and for local areas, was determined with respect to neonatal BCG vaccination.

Based on these data, the reported incidence of tuberculosis in people aged 15 yrs or younger in areas without a policy of neonatal BCG was shown to be significantly higher compared to areas that use neonatal BCG vaccination ($p = 1.5 \times 10^{-5}$ in 1986; and $p = 1.0 \times 10^{-7}$ for 1991). It was estimated that some 646 vaccinations needed to be given to prevent one case of tuberculosis in 1986, and that the figure for 1991 was 551 vaccinations.

This evidence supports a policy of continued neonatal bacille Calmette-Guérin vaccination in the population of the Republic of Ireland at present.

Eur Respir J 1997; 10: 619–623.

Bacille Calmette-Guérin (BCG) vaccine is a live attenuated strain of *Mycobacterium bovis*, which was first used as an antituberculosis vaccine in humans in Paris in 1921. Whilst its use has been recommended by the World Health Organization (WHO) for nearly four decades, results from randomized clinical trials have produced variable results from no benefit to a greater than 70% efficacy [1–4].

The trials in Chingelputt in South India [5], in Georgia, USA [6] and Illinois, USA [7], all suggested little or no efficacy, whereas other trials in poor socioeconomic groups [8, 9] have suggested efficacy of greater than 70%.

It is difficult to reconcile the variable results reported in these studies and, whilst several explanations, including deficiencies in the conduct and design of the trials [10, 11], variable bacteriological characteristics in BCG strains [12], variable results depending on the injection technique used, [9], and variable response depending on whether a liquid vaccine or freeze-dried vaccine is used [13], no conclusive explanation has been advanced.

In a retrospective analysis of 19 case control studies, SMITH [14] also reported a variable protective efficacy similar to that reported with prospective studies. All of these studies have been conducted either in developing Third World countries or among identifiably disadvantaged ethnic groups within developed countries. Mycobacterial vaccines have been reviewed by FINE and RODRIGUES [15] and they concluded that, whilst the current available vaccines were inexpensive, stable, safe and in widespread use, they were less than ideal because of the "unpredictable nature of their protective efficacy in different populations". More recently, FINE [16] suggested

that some of the variation in reported results may be related to environmental and climatic factors, particularly geographical variation in exposure to environmental, nontuberculous mycobacteria. A recent review by COLDITZ *et al.* [17] suggested that latitude might explain some 41% of the variance in published studies on BCG.

There is a national recommendation of neonatal BCG vaccination in the Republic of Ireland but application is not uniform [18]. The uptake of vaccination in areas using neonatal BCG is on average 85% (range 72–92%) based on visible BCG scars. Even in areas which do not have a defined policy of neonatal vaccination, the uptake of the vaccine (again based on visible BCG scars) can average 22% of primary school children [19]. The main factors determining the decision with respect to BCG vaccination are the perception of efficacy and historical usage in the particular area, since the vaccine was first introduced to Ireland in 1954. There has been a steady decline in the incidence of tuberculosis from 1,152 cases reported in 1980 to less than 600 cases per year in the 1990s. The population of the country is predominantly (more than 98%) native European population, in contrast to much of western Europe, where immigration has contributed significantly to tuberculosis incidence [20]. Although a review of vaccination practices [21] did suggest there was benefit, from vaccination in the Republic of Ireland, particularly in terms of tuberculosis meningitis, we felt it was appropriate to have a more comprehensive survey of the experience with respect to BCG vaccination in Ireland.

The aims of the present study, therefore, were to use data from the 1986 [18] and 1991 [22] National Tuberculosis Surveys and the Census of Population for both years to determine whether BCG vaccination policy had

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Keywords: Bacille Calmette-Guérin
childhood tuberculosis
prevention of tuberculosis

Received: December 12 1995

Accepted after revision November 30 1996

any influence on the reported incidence of tuberculosis in the Republic of Ireland.

Methods

Data from the National Census of Population of Ireland for 1986 and 1991 were received directly from the Central Statistics Office. These data were combined with the results of the National Tuberculosis Surveys of 1986 and 1991 to determine incidence of tuberculosis, age distribution of tuberculosis and BCG vaccination policies. This latter information made it possible to divide the country into two subgroups: 1) areas in which neonatal BCG vaccination was the stated policy (Yes BCG); and 2) areas which did not recommend neonatal BCG vaccination (No BCG). The postal survey was conducted after April of the following year (*i.e.* April 1987 for the 1986 survey; and April 1992 for the 1991 survey); the reported number of cases is based on those patients who had definite culture positive tuberculosis or a compelling clinical picture with radiological evidence of tuberculosis and a response to antituberculosis drug therapy.

Both national tuberculosis surveys were postal surveys, in which a questionnaire was sent to every Director of Community Care, every hospital clinical consultant and every microbiology laboratory. To ensure maximum response, nonresponders were resurveyed at 4 and at 8 weeks, and then contacted by telephone. Both surveys were conducted in the same manner. While the Department of Health in Dublin report aggregated national figures subdivided into respiratory and nonrespiratory cases of tuberculosis, they do not produce further analysis and do not provide the necessary information as regards age groups. Nor are the data related to public health area and, therefore, independent surveys were necessary.

Data on General Medical Services (GMS) card holders were used. In Ireland, entitlement to a GMS card, which provides an entirely free medical service including primary care, hospital care and all medications, is income-related. We felt that this would be important, as the socioeconomic group (SEG) categorization used in the national census is a poor tool for our purposes.

Tuberculosis services (surveillance, investigation, diagnosis and treatment, follow-up and contact tracing) are entirely free of charge to all, irrespective of income, under separate specific legislation enacted in 1947.

Data on the distribution of GMS card holders were received directly from the GMS Payments Board, Dublin.

The number of cases potentially prevented by BCG and the number of individuals needing to be vaccinated were calculated by the following formulae:

Cases prevented =

$$\frac{\text{Yes BCG population} < 15 \text{ yrs}}{100,000}$$

× ((rate <15 yrs in No BCG) - (rate <15 yrs in Yes BCG))

Number required to be vaccinated to prevent one case of TB =

$$\frac{\text{Total number of births}}{\text{Number of cases prevented}}$$

Data were compared using Chi-squared analysis and are expressed as p-value, χ^2 value, and relative risk (RR) with 95% confidence limits (95% CL).

Results

The National Tuberculosis Surveys of 1986 and 1991 showed an incidence of tuberculosis of 21.6 (756 cases) and 16.5 (582 cases) per 100,000 population, respectively. In the 1991 survey, there were 14 cases of tuberculosis in which the age was not specified, of which eight were in the neonatal BCG population and six in the non-neonatal BCG population.

Table 1 presents the population distribution by age group from the Census of Population in 1986 and 1991. It also shows the total number of the population and percentage covered by GMS cards. Analysis shows that there was: 1) a significant decrease in the percentage of the population younger than 15 yrs in 1991 ($p < 1.0 \times 10^{-7}$; $\chi^2 = 3051.5$); and 2) that there were fewer individuals covered by GMS cards in 1991 ($p < 1.0 \times 10^{-7}$; $\chi^2 = 5541.45$).

Table 2 summarizes the age distribution and GMS card coverage for areas which use BCG (Yes BCG) and areas which do not use BCG (No BCG) both for 1986 and 1991. For both years, the population age structure is similar but there are relatively more individuals covered by GMS cards in the "No BCG" area.

Two areas (total population 104,018 people in 1991) discontinued neonatal BCG vaccine on January 1, 1989.

Table 1. — Population distribution by age group and the number holding General Medical Services (GMS) cards for the years 1986 and 1991

Age	1986		1991	
	n	(%)	n	(%)
<15 yrs	1021163	(29)	962758	(27)
≥15 yrs	2475708	(71)	2560641	(73)
Total	3496871		3523399	
GMS cards (all ages)	1323038	(38)	1237772	(35)

Figures in parentheses represent the percentage of the total population holding GMS cards or in a specific age group.

Table 2. — Population distribution by age group in BCG and non-BGC areas; the number and percentage covered by General Medical Services (GMS) card

Age	1986		1991		
	No BCG	Yes BCG	No BCG	Yes BCG	
<15 yrs	n (%)	269350 (29)	751813 (29)	282489 (28)	680269 (27)
≥15 yrs	n (%)	663685 (71)	1812023 (71)	744185 (72)	1819456 (73)
Total		933035	2563836	1023674	2499725
GMS	n (%)	393780 (42)	929258 (36)	399536 (39)	838236 (34)

Figures in parentheses represent the percentage of the total population holding GMS cards or in a specific age group. BCG: bacille Calmette-Guerin; Yes BCG: areas in which neonatal BCG vaccination was the stated policy; No BCG: areas which did not recommend BCG vaccination.

In our analysis, we could not show that these areas were significantly different in terms of tuberculosis rate in people <15 yrs for 1991 compared with areas that continue with neonatal BCG vaccination. This is obviously an interesting subpopulation to observe in a future survey.

Nationally, the percentage of population covered by GMS cards declined from 38% in 1986 to 35% in 1991. There was also a small decline in GMS cardholders in each of the subpopulations, suggesting a parallel growth in affluence, since the rules regulating the awarding of cards were not altered in this interval.

The Central Statistics Office in Dublin categorizes the population into 12 socioeconomic groups. The difficulty is that these groups are occupational categories and do not necessarily reflect degree of affluence. During the analysis, we determined that these groupings would not make it possible for us to have a reasonable estimate of affluence and, therefore, we elected to consider the GMS card as a better surrogate for economic status.

Table 3 compares age-specific rates for tuberculosis in 1986, and shows significantly more cases aged <15 yrs in the "No-BCG" population compared to the "Yes BCG" population ($p=1.5 \times 10^{-5}$; $\chi^2=18.77$; RR=1.92 (95% CL 1.47–2.40)). There was no significant difference in incidence in people aged ≥ 15 yrs in the two populations ($p=0.96$).

Table 4 shows that there were significantly more cases with tuberculosis in patients aged <15 yrs in 1991 in the "No BCG" population ($p=1.0 \times 10^{-7}$; $\chi^2=31.95$; RR=2.12 (95% CL 1.75–2.58)) compared to the "Yes BCG" population. The incidence of cases in the ≥ 15 yrs "No BCG" population was significantly higher than in the ≥ 15 yrs "Yes BCG" population ($p=0.052$; $\chi^2=3.76$; RR=1.13 (95% CL 1.08–1.28)). The overall rate in the "No BCG" group was higher ($p=1.5 \times 10^{-4}$; $\chi^2=14.38$; RR=1.25 (95% CL 1.12–1.39)).

Table 3. – Tuberculosis rate per 100,000 population for 1986

		National	No BCG	Yes BCG
Total cases	n	756	220	536
	n/100,000	21.6	23.6	20.9
Cases <15 yrs	n	75	38	37
	n/100,000	7.3	14.1	4.9
Cases ≥ 15 yrs	n	681	182	499
	n/100,000	27.5	27.4	27.5

For definitions see legend to table 2.

Table 4. – Tuberculosis rate per 100,000 population for 1991

		National	No BCG	Yes BCG
Total cases	n	582	211	371
	n/100,000	16.5	20.6	14.8
Cases <15 yrs	n	61	38	23
	n/100,000	6.3	13.4	3.4
Cases ≥ 15 yrs	n	507	167	340
	n/100,000	19.8	22.4	18.7
Age not stated	n	14	6	8

For definitions see legend to table 2.

When the tuberculosis data of 1986 were compared with those of 1991, there was a statistically significant decline in the total number of cases of tuberculosis comparing 1991 to 1986 ($p=1.0 \times 10^{-6}$; $\chi^2=23.97$). There was no significant difference ($p=0.34$) in the number of cases aged <15 yrs. There was a significant decrease ($p=<1.0 \times 10^{-7}$; $\chi^2=31.71$; RR=1.17 (95% CL 1.11–1.22)) in the number of cases aged ≥ 15 yrs when the two years were compared. This suggests that the major part of the decline in tuberculosis was a reduction in cases in individuals aged ≥ 15 yrs.

Between 1986 and 1991, the national rate for tuberculosis declined by 5.1 per 100,000 (from 21.6 per 100,000 in 1986 to 16.5 per 100,000 in 1991). For the population using neonatal BCG, the decline was 6.1 per 100,000 (20.9 per 100,000 in 1986 to 14.8 per 100,000 in 1991). For the population in the no neonatal BCG areas, there was a smaller decline of 3.0 per 100,000 (23.6 per 100,000 in 1986 to 20.6 per 100,000 in 1991).

The national birth rate was 17.4 per 1,000 population for 1986 and 15.0 per 1,000 population in 1991. If we accept the differences in reported incidence of tuberculosis in individuals aged <15 yrs as a BCG effect, then, by using the differences in rate per 100,000 population, we can calculate that without BCG in 1986 there would have been 106 cases of tuberculosis among individuals aged <15 yrs in the population that received BCG vaccination, compared with a reported number of cases of 37, suggesting 69 cases were prevented. Using the same calculation for 1991, we would have estimated 91 cases against an observed 23 cases, giving a possible reduction of 68 cases. Based on the birth rate, we estimate that 646 individuals needed vaccination in 1986 to prevent one case of TB, whereas 551 neonates would require vaccination in 1991.

Discussion

BCG vaccination policy is hotly debated wherever and whenever the subject arises. The problems and dangers which beset most vaccinations are further exaggerated when considering BCG: potential dangers of a live vaccine; the historical disaster of Lübeck; doubts about efficacy and cost-effectiveness; the potential loss of the tuberculin skin test as an epidemiological tool in the surveillance of tuberculosis; the difficulties in implementing national programmes; the great difficulty in measuring outcome in a convincing manner. Many of these factors apply to most vaccines, but since we are dealing with an infection that only results in 5% of the infected population suffering disease in the first year, with a further 5% lifetime risk of manifesting disease later in life, efficacy is more difficult to quantify. Since the disease can affect many organs and mimic many other diseases, precision in diagnosis may be hard to achieve, especially in underdeveloped countries, where the disease is common and resources are scarce. On the other hand, in developed countries where resources are available to carry out properly resourced controlled trials, the incidence of the disease often precludes the expectation of clear-cut outcomes. Nevertheless, despite the methodological difficulties, it is important for countries

using this vaccine to try and estimate any influence it has on the tuberculosis situation in their population.

In the present study, we have asked a simple question and the answer appears to be that the incidence of tuberculosis is greater in children <15 yrs of age in areas which do not use BCG. This cannot be explained by the effect of an immigrant population, which the Republic of Ireland does not have, nor of undue influence of human immunodeficiency virus (HIV), as tuberculosis has not been diagnosed in Ireland in any HIV patient <15 yrs of age. It is not explained by access to medical services, as the main "No BCG" areas are well served by major hospitals and full primary health care services. In fact, there are slightly more patients with GMS cards in the areas which do not use BCG. This population, therefore, has free access to all medical services (in-patient, out-patient, primary, secondary and tertiary). Also, there is evidence that use of the medical services by the GMS card-holding population is greater than by non-GMS card-holders. A GMS card, however, does suggest a lower economic status, which is a recognized factor in tuberculosis, and this may play a part in the present study. The economic differences, however, are not clear-cut.

There are few homeless people and they are mainly in the large cities, particularly in Dublin, which is a BCG area. Likewise, the HIV incidence in Ireland is again mainly in the Dublin [23] area. Some 3–4% of cases of tuberculosis in the whole population are HIV-positive and nearly all of these are in the Dublin area [22].

Previous studies relating to BCG in Ireland have also shown evidence of some protection. SHANNON *et al.* [24], reporting on a school outbreak of tuberculosis in Ireland, showed significant protection against tuberculosis and particularly against miliary tuberculosis and tuberculous meningitis. There was also evidence of benefit reported by the Eastern Health Board BCG Committee [21] and by JOHNSON [25], using analysis based on hospital in-patient enquiry discharge reports. Other reports of mini-epidemics of tuberculosis in the paediatric population [26, 27] in Ireland, while not specifically addressing the value of BCG, do show that more cases of tuberculosis occurred and also that tuberculous meningitis may have been more common in those who had not received vaccination. One report of a school outbreak of tuberculosis in the south of Ireland does not give sufficient data to draw any conclusion about the influence of BCG, but the authors felt that it had not been helpful [28].

The WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) [29] make a number of general recommendations about discontinuation of routine neonatal BCG, concerning elements of the tuberculosis programme and the statistics for incidence of tuberculous meningitis and smear-positive pulmonary tuberculosis. Specifically, they recommend that the average incidence of tuberculosis should be <5 cases per 100,000 per year in three successive years, and that the annual risk of tuberculosis infection should be $\leq 0.1\%$. They also suggest that there should be some 10% decrease in tuberculosis annually for a period of a decade. Furthermore, they strongly suggest that neonatal BCG should not be discontinued until the incidence of childhood tuberculous meningitis is <1 case per 10 million per

year. These criteria have not yet been achieved in the Republic of Ireland.

On the basis of this analysis of data collected in the same way 5 yrs apart, it is clear that a recommended policy of neonatal bacille Calmette-Guérin vaccination is associated with a significantly lower incidence of tuberculosis in children (<15 yrs) in the Irish population. It therefore seems reasonable to continue the Department of Health recommendation of neonatal vaccination until the internationally accepted criteria are achieved, at which time it would be appropriate to reassess its possible influence.

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