

## Houston C (2004). Ferguson's BCG research - Canada's first randomized clinical trial?



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In 1988 I received a letter from Dr David L Sackett, Professor of Clinical Epidemiology and Biostatistics at McMaster University:

*I have become interested in determining whether the first-ever randomized clinical trial in Canada was not, in fact, carried out at Fort Qu'Appelle. I have been corresponding with former associates of the team who carried out the BCG Trial among Canadian Indian Children at Fort Qu'Appelle, but have not, as yet, been able to obtain a copy of the protocol that would tell me whether a formal random allocation procedure was carried out.... It would be nice to show that we Colonials were well ahead of our British colleagues, who regularly take credit for the first randomized clinical trial but did not carry it out until the 1940s.*

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I responded by sending Dr Sackett the paper by RG Ferguson and AB Simes, *BCG vaccination of Indian infants* in Saskatchewan, published in *Tubercle*, Volume 30, pages 5-11 (1949).

Dr Sackett responded:

*What I have been trying to tease out over the last couple of years is the meaning of the paragraph at the top of page 2, where they state 'one member of each such pair was allotted at random to one of two groups'. The term 'at random' remains ambiguous, since it could either denote a formal randomization process or a haphazard assignment ... This may be the first randomized trial ever conducted in Canada, and if so it would of course pre-date the British antibiotic trials of the late 1940s that are generally acknowledged as the first randomized trials in humans. It would therefore be very nice to give credit to Drs Ferguson and Simes for their pioneering work.*

Ferguson had recognized Indians as the Saskatchewan group most likely to benefit from BCG. Compared to whites, Indians in 1926 were ten times more likely to die from TB (and in 1936 the death rate for Saskatchewan Indian infants in the first year of life was still 1603 per 100,000). In Ferguson's eyes the slight theoretical risk from the use of BCG was justified.

In 1931, the Associate Committee on Tuberculosis of the National Research Council (NRC) received a favourable report from its subcommittee on BCG, and the next year Ferguson received approval to begin BCG vaccination of newborn infants in the Fort Qu'Appelle Health Unit; his annual NRC research grant was raised to \$4500, which represented a substantial share of the \$28,900 allotted for tuberculosis research in Canada.

In the prospective BCG study, published by Ferguson and Simes in 1949, families of comparable status in respect to housing, sanitation, and certain other economic and social factors likely to affect the health of children were paired, and one family of each such pair was allotted 'at random' to one of two groups, designated 'Group A' and 'Group B'. All children born into the families of Group A were vaccinated in one year, while all children born into families of Group B in the same year were taken as controls. In the following year this situation would be reversed, and so on throughout the study. Vaccination of every second infant, carefully matched, was crucial to the integrity of the results. Ferguson phoned Dr Austin Simes at the nearby Indian hospital at least once each week to get a list of the births and to ascertain whether each newly born infant was placed in the BCG group or the control group. Simes and Ferguson had been medical classmates; each received his M.D. from the University of Manitoba in 1916.

For the first 21 newborn infants, in 1933, BCG vaccine was administered in a teaspoon with a little lukewarm milk, half an hour before feeding, three times at 2-day intervals in the first ten days of life. If the mother was known to have tuberculosis, the infant was kept separate from the mother for six weeks. Beginning in 1934, BCG was administered

intracutaneously, and the initial dose of 0.3 mg soon reduced to 0.2 mg. Oral revaccination was performed at one and three years of age, again in three doses at 48-h intervals.

Covering letters from Dr Armand Frappier at the Faculté de Médecine, Université de Montréal, show that each batch of BCG vaccine had been tested aerobically and anaerobically, and that the "200 guinea pigs vaccinated since last January" [1933] were "feeling better and better" as "witness to the purity of the strain" (Houston 1991). Between 1933 and 1945, Ferguson and Simes vaccinated 306 Indian infants at birth and another 303 served as controls. Altogether 212 families were involved but no breakdown of these families into the two groups is extant. Nowhere is there mention of the mechanism for handling twins but twins are rare among Cree Indians. Each child was examined annually and a tuberculin test given. Whenever a tuberculin reactive was negative, revaccination was carried out at 3-year intervals. By 1947, the unvaccinated were nearly five times as likely to manifest tuberculosis (29 vs 6), and the disease was more severe, more widely spread throughout the body, and caused more deaths (9 vs 2) than in the vaccinated group. Post mortem examinations were performed whenever possible and included 64% of the fatalities among the vaccinated group. There was no evidence whatever of any recurrence of virulence of the BCG strain in the vaccinated group, a theoretical possibility greatly feared by experts in the United States and elsewhere.

Ferguson's long-term BCG research was supported financially by the National Research Council for 23 years. His studies ceased only when he retired. Armand Frappier has said that this was the first intensive and prolonged BCG study in the world to be supported officially. When Ferguson died in 1964, Dr Boughton paid tribute to his work with the BCG vaccine:

*No record of Dr Ferguson's place in the history of Saskatchewan would be complete without reference to his introduction of the preventive vaccination against tuberculosis by BCG (Bacillus Calmette Guérin). He had taken me with him to see the groundwork being done in Paris by the originating physicians at a time when it was scorned in Great Britain and hardly known in North America. Already, having an intimate knowledge of tuberculosis among the Qu'Appelle Indians, he saw at once the possibility of controlling their tuberculosis. However, in tuberculosis circles there was much questioning about the safety and the morality of introducing live tubercle into the human body ..... But his reasoning and his faith told him he was right so he vaccinated his own children. ('I also vaccinated my children before vaccinating others.') Since there were no untoward results he introduced a BCG vaccination program among the infants in the Qu'Appelle Health Unit. Five years later infant deaths from tuberculosis were only 20% of what they had been. In recent years all Canadian Indian infants which can be reached are vaccinated with BCG. Then came the protection of sanatorium employees and the nurses in eight general hospitals. More recently the World Health Organization has initiated vaccination programs in the developing and underdeveloped countries (Boughton 1964).*

If Austin Simes had used the simplest of all randomizing methods, flipping of a coin, the BCG study might merit recognition as the first truly randomized medical research study in Canada or perhaps anywhere (except for studies such as those of James Lind who tried different scurvy remedies on small groups of men). Indeed, Ferguson and Simes, when they published their results in 1949, stated that theirs was a randomized study. It was therefore with some considerable interest and high expectations that I spent a day studying the original documents in the National Research Council (NRC) archives in Ottawa. An anonymous history in the NRC archives stated that BCG was 'a highly controversial subject' which 'occasionally resulted in acrimonious discussions', although Ferguson's studies, in which Dr AB Simes collaborated, were carefully laid out by members of the NRC statistical staff and results were analyzed by them.

Although Ferguson was usually careful in his choice of words, minutes of the NRC's Associate Committee on Tuberculosis for June 17, 1936, contain statements that negate any such claim:

*It was found more convenient to vaccinate the children born in the hospital and for that reason the greater proportion of the controls had been born in the home.*

Furthermore, reference to a progress report of BCG research by Ferguson and Simes in 1941 showed that the statement in their paper concerning the division into group A and B families was not completely accurate. At the advice of the statisticians at the NRC, this method of randomizing began only on 1 October 1940. Prior to that, alternate births were vaccinated (Ferguson and Simes 1941). Thus Ferguson's studies fail to meet the modern definition of randomization and do not qualify as a truly randomized trial.

Nevertheless, the Panel on Tuberculosis of the NRC Associate Committee on Medical Research in 1946 correctly recognized Ferguson's study as 'the most scientific trial of BCG yet made', and the War History of the Associate Committees of the NRC gave credit to Ferguson's BCG study as 'an experiment which is probably unique in the similarity of its experimental and control groups', praising the 'unusual degree of medical control and the stable habits of the Indians' which made this possible. From an international perspective, Ferguson and Simes' study was methodologically sophisticated for its era.

C Stuart Houston is Professor of Medical Imaging, University of Saskatchewan. He has written *R.G. Ferguson, crusader against tuberculosis*, published by Hannah Foundation/Dundurn Press in December, 1991. This article contains, with permission, quotations from the book.

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