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In 1939, Pearl Kendrick and Grace Eldering reported the results of a field trial of a new pertussis vaccine that the two women had developed at the Michigan Department of Health.[1] The trial had run for more than three years (March 1934 to November 1937), enrolling 5815 children. The vaccinated group 'was made up of all children of acceptable age and history who presented themselves at the city immunization clinics for pertussis vaccination.' The control group 'was selected at random' from a list of non-immunized children maintained by the Grand Rapids City Health Department, producing an 'approximately equal sample of children of the same age, and in the same districts as the injected children.'[1] Based on a careful and innovative analysis of events/person-years at risk, the authors concluded that 'substantial protection had been afforded to the injected group':

> '. . . there were 2.3 annual attacks per 100 [person-years] in the injected group and 15.1 in the control group. Expressed statistically, the difference is equal to fifteen times the standard error, indicating that the probability of such a difference occurring by chance alone is one in several million trials.'[1]

Methodologically, the original field trial design was flawed. The experimental group was self-selected and only control subjects were randomly chosen. Despite careful attention paid to case detection and diagnosis, 1603 observations from the study's early years had to be excluded from the final analysis. Several features of the trial nonetheless make it an important contribution, not simply to the development of an effective pertussis vaccine, but to the history of controlled trials:

(1) The trial was enabled at the height of the Great Depression by a diverse coalition of governmental (local, state and federal) and private agencies, whose activities were orchestrated by Kendrick and Eldering;[2]
(2) The trial was unusual for the level of attention given to case diagnosis and follow-up, and to the discussion of unknown factors which might have biased the results;
(3) A similar level of detail was given in reporting on the analysis and the methodological limitations of the field trial;
(4) It introduced to clinical trials a methodology (events/time analysis) more commonly found in observational epidemiology;
(5) The trial provided an influential network of specialists in public health and biostatistics an occasion to articulate their views of what constituted a 'well-controlled' trial.

PERTUSSIS VACCINES: A BRIEF HISTORY

In 1913, Charles Nicolle introduced the first in a series of pertussis vaccines developed over the next two decades.[3] Few of these vaccines produced consistent results, leading the Council on Pharmacy and Chemistry of the American Medical Association to withdraw its approval from all commercially produced vaccines in 1931.[4] Pertussis was then increasingly a dominant cause of childhood mortality, outranking diphtheria, scarlet fever and measles in many European countries.[5] In the late 1920s, Danish researchers, armed with a better understanding of the antigenic properties of different pertussis strains, had introduced a new generation of vaccines. These European reports of favourable results sparked renewed North American interest in vaccine development: Lewis Sauer, Pearl Kendrick and James Doull were among the researchers who began experimenting with new techniques for developing a more potent, clinically consistent pertussis vaccine.[6] Vaccine evaluation had not followed suit. Existing studies had 'been carried on in the medical literature with slight regard for properly controlled experimentation.'[7]

THE INVESTIGATORS, THE COMMUNITY AND THE TRIAL

Born in 1890, Pearl Kendrick spent several years after college teaching high school science in New York State. She worked briefly at the New York State Department of Health before moving to the Michigan department in 1920, where she worked with Reuben Kahn in developing a new diagnostic assay for syphilis. Six years later, she took charge

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of the Department's Western Michigan Laboratory. In 1932, she received a ScD in bacteriology from the Johns Hopkins School of Hygiene and Public Health.[8,9] On her return to Michigan she asked CC Young, state Director of Laboratories, for permission to work on 'whooping cough'; he allegedly replied 'If you are having any fun working on whooping cough, go ahead.'[10] Accompanied by bacteriologist Grace Eldering, who had joined the Department's laboratories in 1928, Kendrick 'set out' every day after 'the laboratory closed' to collect *Bordetella pertussis* specimens. As Eldering later put it:

> 'We learned about the disease and the depression at the same time. Many of the families were very poor and their living conditions pitiful . . . We listened to sad stories told by desperate fathers who could find no work. We collected specimens by the light of kerosene lamps, from whooping, vomiting, strangling children. We saw what the disease could do. In the laboratory we isolated the pertussis bacillus, not from every patient, but from most of them in the early stages of the disease . . . The cultures were saved and studied in every possible way.'[10]

The Michigan department was one of the few public health laboratories in the USA with a program in vaccine development and production.[a] With CC Young's encouragement, Kendrick and Eldering began working on a pertussis vaccine. The two bacteriologists had closely followed the new literature concerning the importance of using recent bacterial cultures to cultivate pertussis vaccine. By January 1933, they had prepared their first samples,[10;b] and by mid-year they were drawing up plans for an elaborate field trial in Grand Rapids, Michigan.

The Great Depression was perhaps the worst time in recent history to start a large, complex clinical trial: local government funding for public health, never magnanimous, was sharply curtailed.[9] Kendrick cobbled together financial support from federal emergency relief programs, state and city health departments, city government and private donors. Official funds were supplemented with volunteer labour (nurses, technicians, and private physicians) who worked well beyond a paid forty-hour week in preparing, testing, and administering the vaccine. Even so, periodic funding crises hampered case follow-up and record keeping for the study.[10;c]

Trained as laboratory researchers in bacteriology, neither Kendrick nor Eldering had any prior experience with clinical trials. The trial's design and procedures were a work in progress, modified as operational and analytical difficulties became apparent. Crucial to all versions of the study was a federally funded 1934 'pre-school immunization survey' for Grand Rapids, which identified the exposure history of the city's population of children under five years old. The initial plan called for vaccine to be given to a test group of 'non-immune' children 'exposed in their own home,' with controls ideally to be chosen from other children in the same family. When it proved impossible to reach 'exposed' children with the vaccine before they became symptomatic, a more elaborate procedure was adopted.

The experimental group consisted of children who voluntarily came to the city's health clinics to be inoculated. The control group was drawn from non-immune children 'from the same district' in the city as the vaccinated child.[d] Nurses from the Grand Rapids Health Department assigned to one or more of its 18 health districts did the follow-up to identify cases of whooping cough among study participants.[1,10] Initially, the nurses also selected children for the control group; this task was later transferred to Kendrick's office, which relied on the immunization survey. The initial emphasis on selecting controls from the families of inoculants was similarly dropped over time.[e] In October 1935, Kendrick and Eldering presented their preliminary results at the annual American Public Health Association meeting. Of 1592 children enrolled at that time (712 in the 'test group'; 880 controls), there were 63 cases of whooping cough in the control group, and only three in the vaccinated group.[11]

Such favourable results contrasted strongly with the experiences of other American researchers, especially a contemporaneous Cleveland study being led by James Doull. In 1936, Doull and his colleagues[12] were conducting a controlled study of their pertussis vaccine, enrolling children 6–15 months old who visited the city's free milk distribution centres. Assignment was by alternation: the first eligible child was offered vaccination, the second served as a control. Because of substantial losses to enrolment (refusals, drop-outs, and doubtful pre-trial histories of exposure), they soon switched to a 2:1 assignment ratio, with every third eligible child serving as a control. After 979 children had been enrolled, they were unable to detect any advantage for the vaccine: 61 cases among 483 children (test group) versus 71 cases among 496 children (247 controls plus 249 refusals).[12]

Doull had considerable standing in the public health research community: he was Professor of Hygiene at Western Reserve University, a former Associate Professor of Epidemiology at the Johns Hopkins School of Hygiene, and first author of a randomized trial assessing the effects of irradiation with ultraviolet light on the incidence of the common cold.[13] Against a background of scepticism generated by disappointments with earlier pertussis vaccines, the differences between Doull's preliminary findings and Kendrick's results presented a problem for public health authorities. Among the differences between the two studies, children in Doull's trial were markedly

younger (<15 months old), he relied more heavily on physicians for diagnosis of cases, and fewer children (435) were enrolled. Importantly, Doull selected vaccine and control children from the same pool—infants attending Cleveland's milk distribution stations.[12]

Senior figures at the American Public Health Association (APHA) Committee on Administrative Practices—headed by Haven Emerson, former New York City health commissioner and dean of the Columbia School of Public Health—soon found themselves involved in complex negotiations to assess the strengths (and weaknesses) of Kendrick's ongoing field trials. The Committee, engaged in evaluating a variety of existing public health practices, did not want to endorse an inadequately tested vaccine.

THE CONSULTANT

Although Doull did not present his findings publicly until the 1936 meeting of the APHA, he was already in touch with Kendrick about their conflicting findings.[f] Early in 1936, they had discussed the possibility of meeting with Wade Hampton Frost, Professor of Epidemiology at Johns Hopkins, to review their respective studies. His personal status as America's premier epidemiologist aside, Frost was not an obvious choice to advise on vaccine field trials: he was known mainly for his pioneering work in observational studies of polio, influenza and tuberculosis.[14] Frost's other main activities included the development of the Eastern Health District and Hagerstown community studies, and work on the mathematical modelling of epidemics, done in collaboration with statistician Lowell Reed.[15,16]

Kendrick was nonetheless enthusiastic about getting Frost's advice: help that Frost was not eager to provide. Whether because of the press of other work, because of his close relationship with Doull, a former student and colleague, or for some other reason, Frost was reluctant to get involved. Thus, in a letter to Kendrick, he wrote:

> 'I cannot think that any judgment other than Dr Doull's or your own is really needed for interpretation of your data, and on general principles, I think those who know the data most intimately are best qualified to interpret them.'[g]

APHA leaders appealed to Frost to intervene: in addition to Haven Emerson, these included George Ramsey, head of communicable diseases at the New York State Department of Health, previously at the Michigan department and, like Doull, a former student and colleague of Frost's. The APHA committee overseeing immunization practices was deadlocked. According to Ramsey, Doull himself 'is convinced that the Cleveland study has been so carefully and well done that the matter is settled.'[h]

Over the summer and early fall, Frost was reluctantly drawn into discussions about Kendrick's trial. Still, he continued to hope that the issue could be resolved without a site visit:

> 'I very strongly suspect that Miss Kendrick's field studies are not set up in such a way as to give a really good control . . . Not 1 out of 10—perhaps not one out of 50—attempts is successful and as a mere matter of probability the odds are strongly against Miss Kendrick's experiment being sound. If this is the case it may be that her own account of her procedure, which I hope to have from her in writing, will show some basic defect. In that case, it will not be necessary for anyone to go to Grand Rapids.'[i]

In the event, Frost went to Grand Rapids twice (in November 1936 and September 1937), and offered a detailed critique of the trial and a plan for analyzing the results. Frost identified several key issues:[j]

(1) Owing to the long, slow build-up of the trial, the study population overall was quite heterogeneous. Frost recommended dropping the children vaccinated by private physicians, whose records were less reliable than those from the city clinics.
(2) Similarly, in the early years of the trial, follow-up of control children was either inadequate or the records were incomplete. Frost ultimately recommended that the first 1100 observations be dropped from the analysis.
(3) Because recruitment to the trial varied over the life of the study, as did the frequency of nursing visits to look for whooping cough, Frost suggested examining the data using an innovative event/time analysis, which would calculate the number of months each child (vaccinated or control) was at risk for developing pertussis. In keeping with the event analysis, Frost proposed that a child might be a control subject one month and an experimental subject the following month, if they happened to receive the vaccine in the interim.
(4) The possibility of unknown differences between experimental and control groups, because of differences in the way they had been recruited, continued to trouble Frost. He pushed hard for any analyses which would comfort a suspicious mind like his. For example, were rates of other communicable diseases also lower in the experimental group (as might be expected if the vaccinated children were from a higher socio-economic group than the controls)? Kendrick made the recommended comparison of non-pertussis disease incidence, but found no differences between the groups in levels of other childhood infectious diseases.[1]

Nor was Frost alone in his concerns about the trial's design. Harvard statistician Edwin Wilson, drawn into the discussion by George Lawson, a Harvard alumnus involved in pertussis research, sympathized with Frost's reservations. As Wilson commented, there were some observable differences between the experimental and control groups. They might be important but then again they might not be:

> '. . . one can never be certain but what such a difference has some significance with respect to some hidden factor which makes the controls not a fair control… I can see how a cautious person like Frost might think that you weren't getting enough to pay to go on.'[k]

Whatever his initial reservations, it is clear from the tone of Frost's correspondence that his professional regard for Kendrick's commitment to analytical rigor increased considerably over time, as did his regard for the Michigan data.[l] As he wrote to Haven Emerson:

> '. . . considering the circumstances under which the work had to be done—beginning on a small scale and expanding as new funds permitted—I do not see how the complications could well have been avoided. The effect of all these circumstances is that eventual analysis of the material must be considerably more complicated than is required, for instance, in Dr Doull's much simpler material. However, the records are such as to permit such analysis as may be required and, though the statistical work involved will be somewhat laborious, I see no reason why the end result should not be definite.'[m]

In consultation with Kendrick, Eldering and a medically qualified epidemiologist, FC Forsbeck, Frost worked out a detailed plan for analysing the data.[n] The ensuing statistical work was laborious; the investigators produced a 30–plus page codebook detailing the handling of each record. After deciding which records could be used, the investigators had then to transfer the data for 5815 patients, month by month, to punch cards in order to accomplish Frost's event-time analysis.[o]

Frost was among the many individuals, outside and inside the Michigan department, who received a draft of the paper for comment.[p] The published paper followed meticulously Frost's memoranda about analysis and reporting of the trial data, and his guidance was graciously acknowledged (although one could not possibly guess the extent of his contributions from this note). By the time the report was published in May 1939, Frost, its invisible co-author, had died, the victim of an oesophageal cancer that had appeared after his September 1937 visit to Michigan.

Publication of Kendrick and Eldering's paper did not resolve questions about the value of pertussis vaccine. There was general agreement in the specialist community that a replication of Kendrick's study was desirable. Kendrick, in collaboration with James Doull, worked out a proposal for a new field study, which APHA leaders proved reluctant to fund, preferring to wait on corroboration from other, smaller community studies.[q] The technical design of pertussis vaccines was, in any case in rapid evolution, and it was left to Kendrick and other researchers to conduct field trials of newer vaccines in the 1940s and 1950s.[17–22]

The individuals involved in the pertussis field trials of the 1930s—Pearl Kendrick, Grace Eldering, Wade Hampton Frost, James Doull, *et al*.—do not figure in any of the standard histories of clinical trials.[23–27] Yet Kendrick's skill in assembling the people and money to conduct a large field trial in the midst of the Great Depression[2] is as remarkable as her dedication to finding out whether her vaccine really did work. In addition to her response to Frost's criticisms, time and again, Kendrick welcomed close scrutiny of her data.[r] The 1934 pertussis vaccine trial launched her national career in vaccine development and standardization, which continued for many decades.[10,28] Among her many accomplishments was the development of the mouse protection test, which had a long international history as a measure of vaccine potency.[22,29,30]

The most surprising character to figure in this story remains Wade Hampton Frost. Unlike other epidemiologists and biostatisticians of his generation—Edgar Sydenstricker, Edwin Wilson, Major Greenwood—Frost never wrote a line about experimentation, controlled or otherwise. Yet it is clear from the record of his encounters with Pearl Kendrick that he had a profound appreciation of the importance of controlled comparison in any epidemiological analysis. And he offered to Kendrick and Eldering the methodological fruits of his epidemiological studies of tuberculosis, influenza and polio. For Frost, in any epidemiological analysis, it was crucial to reliably capture the period over which events occurred.[31] While Frost did not invent the methodology of 'event/person-years' analysis,[32] he had a profound appreciation for defining the period at risk in any epidemiological analysis, including Kendrick's field trial of pertussis vaccines.

Several years after Kendrick and Eldering's field trial, Joseph Bell, another epidemiologist trained at Johns Hopkins, published a field trial of a new pertussis vaccine developed by the US Public Health Service. Bell's study avoided many of the pitfalls in design which had hampered earlier field trials, giving careful attention to random selection of experimental and control groups and to avoiding the effects of ascertainment bias in follow-up of results.[33,34] It is not possible to establish whether Bell had

direct contact with Frost during his initial time at Johns Hopkins. We do know that Frost's preferred method of teaching was the 'laboratory problem', in which students would work through the planning and analysis of an epidemiological study, discussing methodological issues as they proceeded.[15] Whether directly or indirectly through one of Frost's colleagues, it seems likely that the lessons of Frost's experience with Kendrick's field trial were passed on.

Neither Frost nor Johns Hopkins appear in the standard histories of clinical trials, most of which refer to RA Fisher and Austin Bradford Hill, British statisticians, the British Medical Research Council, and/or the long tradition—as illustrated by the records published in the James Lind Library—of medical investigators seeking 'fair' and objective tests of therapies. Yet in retrospect, it is noticeable how many innovative studies of the 1930s and 1940s were conducted by individuals with a strong connection to Wade Frost and/or to his Johns Hopkins colleague, the statistician Lowell Reed. In 1931, James Doull had conducted a randomized trial to assess whether ultraviolet light would reduce the incidence of common colds, using, on Reed's advice, an innovative urn device to assign patients to experimental and control groups.[13] Carroll Palmer guided the US Public Health Service randomized trial of streptomycin,[35] which was conducted contemporaneously with the more famous MRC study.[36] And Margaret Merrell was statistician for the wartime penicillin clinical evaluations and a prominent post-war advocate and popularizer of controlled clinical trials in North America.[26] Along with Wade Hampton Frost's role as Pearl Kendrick's mentor in analysing her 1934 field trial of pertussis vaccine, they suggest the existence of a strong and hitherto unacknowledged network in the development of clinical trial methodology and practice.

Competing interests None declared.

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ENDNOTES

a On the Michigan laboratory under Young, see Allen (1979), pp. 7–29.[9] Other health departments with active research programs would include Massachusetts, New York State and New York City. See Rosenkrantz BG (1972) and Sexton AM (1967).[37,38]

b Pearl Kendrick to Louis Sauer, 12 June 1934. Box 1, Grace Eldering papers.

c Pearl Kendrick, The Status of the Study of Whooping Cough in Grand Rapids, 10 December 1934; Pearl Kendrick to CC Young, 27 August 1935, both Box 14, Michigan Department of Health; Landmarks in Pertussis Immunization Study, 1932–1935; Pearl Kendrick to Wade Hampton Frost, 15 September 1937, both Box 4, Kendrick papers.

d Michigan Department of Health, Bureau of Laboratories, Whooping Cough Prevention Study, 1–20–34; idem, Whooping Cough Prevention Study, General Plan, revised 10–16–34; idem, Whooping Cough Prevention Study, 10–13–1936, all Box 4, Kendrick papers; Pearl Kendrick to CC Young, 18 February 1933, Box 14, Michigan Department of Health.

e Michigan Department of Health, Whooping Cough Prevention Study, 13 October 1936, Box 4, Kendrick papers.

f James Doull to Pearl Kendrick, 25 April 1936. See also Doull to Kendrick, 2 March 1936; Kendrick to Doull, 13 May 1936, Kendrick to George Ramsey, 30 September 1936, all Box 3, Kendrick papers.

g Wade Hampton Frost to Pearl Kendrick, 2 February 1936, Box 3, Kendrick papers.

h George H. Ramsey to Wade Hampton Frost, 27 August 1936; Kendrick to Frost, 26 February 1936, Box 3, Kendrick papers; Haven Emerson to C.E.A. Winslow, 18 November 1935; Series 1, Box 9, Winslow papers.

i Wade Hampton Frost to George H. Ramsey, 10 September 1936, Box 3, Kendrick papers.

j Wade Hampton Frost to Pearl Kendrick, 10 August 1936, 24 October 1936, 21 September 1937; Suggestions for Revising Records and Procedures, dictated by Dr. Frost, 12 November 1936; Whooping Cough Immunization Study. Directions for Sorting and Revising Records, 15 September 1937 pursuant to advice of Wade Frost; [WHF], Memorandum for Dr. Kendrick, 18 September 1937; Frost to Kendrick, 21 September 1937 [Boxes 3 and 4, Kendrick papers].

k Edwin B. Wilson to George M. Lawson, 19 November 1937 [Box 3, Kendrick papers]. Lawson, who had written a Harvard thesis on pertussis, strongly supported Kendrick and had written Wilson for his advice: see George Lawson to Edwin B. Wilson, 27 October 1937. For further discussion of the adequacy of the controls, see Lawson to Wilson, 22 November 1937 and Wilson to Lawson, 26 November 1937. All in Box 2, Wilson papers.]

l Wade Hampton Frost to Grace Eldering, 17 November 1936, 21 September 1937; Pearl Kendrick to Wade Hampton Frost, 7 October 1936, 24 November 1936; Eldering to Frost, 25 November 1936. All Box 3, Kendrick papers.

m Wade Hampton Frost to Haven Emerson, 12 September 1936, Box 4, Kendrick papers.

n Frost remained anxious about having a medically qualified epidemiologist—Forsbeck—supervise the data analysis. See George H Ramsey to CC Young, 13 April 1937; Young to Ramsey, 15 April 1937. Box 3, Kendrick papers.

o Code Manual, Definitions and Explanations. A Study in Active Immunization Against Pertussis. Michigan Department of Health, Bureau of Laboratories, Western Michigan Division [undated]; Pearl Kendrick to Clark Tibbetts, 3 November 1937. Box 14, Michigan Department of Public Health.

p Pearl Kendrick to C.C. Young, 15 September 1938, Box 14, Michigan Department of Public Health.

q Report of the Subcommittee on Evaluation of the Committee on Administrative Practices, [1938], Series III, Box 42, Winslow papers; George Lawson to Pearl Kendrick, 22 November 1937; Pearl Kendrick to James Doull, 13 September 1938, Box 4; Haven Emerson to Pearl Kendrick, 12 March 1938, Box 6, Kendrick papers.

r See also her comments re EB Wilson's somewhat sceptical letter: Pearl Kendrick to George Lawson, 30 November 1937. Box 4, Kendrick papers.

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