Considering factors that may influence protective results of vaccination

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Vaccine effectiveness

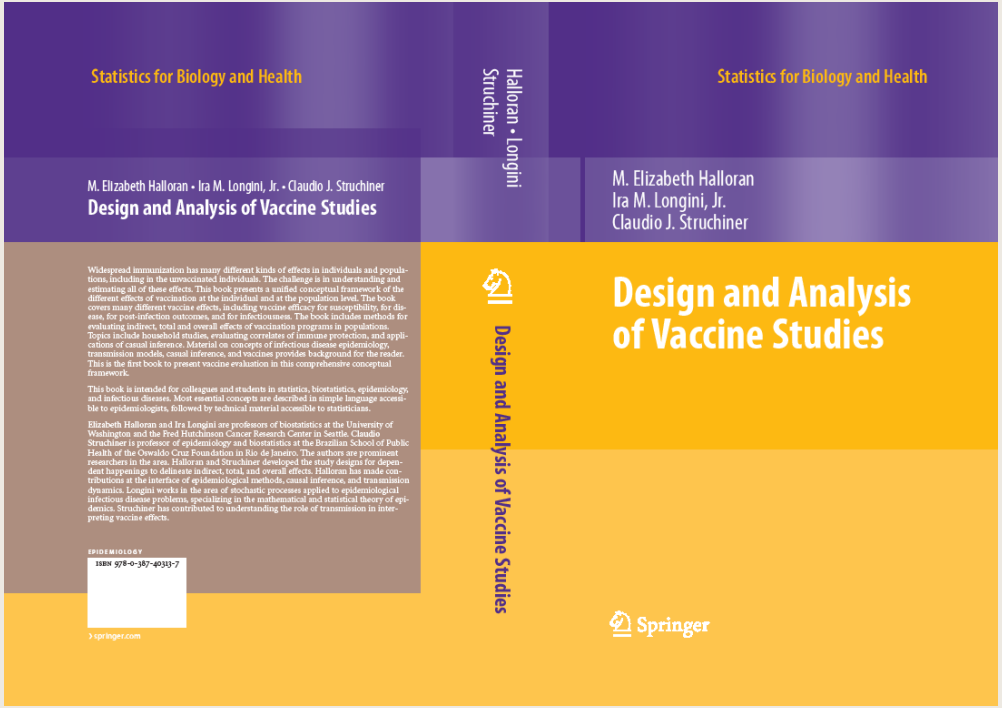
- Generally estimated as one minus some measure of relative risk, RR, in the vaccinated group compared to the unvaccinated:

$$VE = 1 - \frac{Risk\ vaccinated}{Risk\ unvaccinated} = 1 - RR$$

- The groups being compared could be composed of individuals or of populations or communities

Design and analysis of observational studies for estimating vaccine effectiveness go back to the early 1900's

Summarized in:



Section of Epidemiology and State Medicine.

June 4, 1915.

Dr. W. H. Hamer, Vice-President of the Section, in the Chair.

The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general.

By Mr. Major Greenwood, jun., and Mr. G. Udny Yule.

Introduction.

Hardly any subjects within the range of preventive medicine are of more immediate importance than the methods of prophylaxis which ought to be adopted with respect to typhoid fever and cholera.

Typhoid fever has already been responsible for much illness and many deaths in nearly all the armies on active service, while cholera has taken toll of one at least of our enemies and one of our allies. Further, our troops are now fighting in a part of Europe and Asia which has always been a favourable soil for the development of epidemic cholera and was recently the scene of outbreaks among troops actually engaged in the present war.

Major Greenwood
1880 –1949

G. Udny Yule
1871 – 1951

Conditions necessary for valid inference

1. “The persons must be, in all material respects, alike.”
2. “The effective exposure to the disease must be identical in the case of inoculated and uninoculated persons.”
3. “The criteria of the fact of inoculation and of the fact of the disease having occurred must be independent.”

Examples of estimates they made

TABLE I.—ANTI-TYPHOID COMMITTEE'S DATA.

First arrangement.

	Not attacked	Attacked	Total
Inoculated	10,322	56	10,378
Not inoculated	8,664	272	8,936
Total	18,986	328	19,314

$\chi^2 = 180{\cdot}38$. P = less than 0·0001.

$$VE = 1 - \frac{\frac{56}{10378}}{\frac{272}{8936}} = 1 - \frac{0.0054}{0.0304} = 0.82$$

Further estimates of VE for smallpox deaths

largely used by Macdonell, Maynard, and others. One or two such tables were given by Professor Pearson in his original memoir on the method (1900, ii) and a table for deaths amongst vaccinated and unvaccinated small-pox patients is headed in the following form :—

TABLE XLIII.

Degree of effective vaccination	Strength to resist small-pox when incurred: Deaths	Recoveries	Total
Cicatrix absent	94	383	477
Cicatrix present	42	1,562	1,604
Total	136	1,945	2,081

VE = 0.87, $p < 0.0001$

A STUDY IN ACTIVE IMMUNIZATION AGAINST PERTUSSIS[1]

By

PEARL KENDRICK AND GRACE ELDERING

WITH STATISTICAL ANALYSES OF THE DATA BY ANTHONY J. BOROWSKI

(Received for publication January 25th, 1939)

The present study of pertussis immunization in Grand Rapids had its beginning in 1932 when a study of the practicability of laboratory diagnostic methods in pertussis was undertaken. The relative uniformity with which *H. pertussis* could be isolated during the first weeks of disease under properly controlled conditions emphasized the etiological association of the organism with the disease and raised the question as to why attempts to produce active immunization with pertussis vaccine had given such irregular and inconclusive results. In February, 1933, a study series was started to observe the protective effect of pertussis vaccine given to a child after exposure to pertussis in his own household but before the development of symptoms. The administrative problem was so complicated and the interpretation of results so difficult that toward the latter part of the year this plan was abandoned in favor of a study of the protective value of vaccine completely administered prior to exposure. Also this seemed a more fundamental approach to the public health problem of pertussis control. A progress report on the preventive study was made by the authors (1) in January, 1936, after which the series under observation was extended. On November 1, 1937, the records were closed for purposes of compilation and analysis.

Since the publication of the authors' progress report, several papers have been added to the literature on the use of "Phase I" or "smooth" *H. pertussis* suspensions as vaccine for pertussis immunization. Among these, Doull, Shibley and McClelland (2) reported a study in Cleveland in which the distribution of pertussis attacks was not significantly different in the vaccine-injected and control groups. Silverthorne and Fraser (3) recently reported two attacks of whooping cough among 747 vaccinated children compared with 23 attacks among 161 controls. Singer-Brooks (4) and Miller (5) present data which show a higher degree of protection in a vaccinated group than in a control group. Sauer (6) has reaffirmed his finding of protection following the use of pertussis vaccine. Madsen (7), basing his opin-

[1] From the Michigan Department of Health, Bureau of Laboratories, Western Michigan Division, Grand Rapids, Mich.; with the co-operation of the City Health Department of Grand Rapids, John L. Lavan, M.D., Health Officer; Fred Miller, M.D., School Physician in charge

Pearl Kendrick
1890 –1980

Grace Eldering
1900 –1988

The importance of conditioning on types of exposure

TABLE 12

Persons in the study series exposed to pertussis according to "type" of exposure and proportions of those exposed who were attacked

	Classification according to history of exposure				No history of exposure
	Definite in own household	Definite in other household	Indefinite	Total	
Both groups					
No. of exposures...	243	161	166	570	3642
Attacks.....	172	39	14	225	175
Per cent.....	70.8	24.2	8.4	39.5	4.8
Vaccine group					
No. of exposures...	83	100	114	297	1518
Attacks.....	29	5	4	38	14
Per cent.....	34.9	5.0	3.5	12.8	0.9
Control group					
No. of exposures...	160	61	52	273	2124
Attacks.....	143	34	10	187	161
Per cent.....	89.4	55.7	19.2	68.5	7.6

$$VE_{SAR} = 1 - \frac{\frac{29}{83}}{\frac{143}{160}} = 1 - \frac{0.349}{0.894} = 0.61, p < 0.0001$$

1954: Salk killed poliomyelitis field study in the US in 1,829,916 children nationwide

T Francis, RF Korns, RB Voights, M Boisen, FM Hemphill, JA Napier, and E Tolchinsky. An evaluation of the 1954 poliomyelitis vaccine trials. *Am J Pub Health*, **45**:1 – 63, 1955.

JOURNAL OF THE AMERICAN STATISTICAL ASSOCIATION

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STATISTICS OF THE 1954 POLIO VACCINE TRIALS*

K. A. BROWNLEE
University of Chicago

THE *Report* on the 1954 Poliomyelitis Vaccine Trial was produced by the Poliomyelitis Vaccine Evaluation Center at the University of Michigan, directed by Thomas Francis with Robert Korns as Deputy Director and Robert Voight as Chief of Statistical Operations. Apparently the *Report* is a joint product of the staff of the Evaluation Center.

The *Report* was launched upon the world with a volume of publicity probably unprecedented for a scientific work. The *Report* was used by the National Foundation for Infantile Paralysis to push the vaccine into mass use in the spring of 1955. The fact that the vaccine then being pushed differed very importantly from that used in the 1954 trial, in that it did not contain merthiolate, was released to the public only after the fact that some of the vaccine was causing poliomyelitis could no longer be ignored. The ultimate horror came when the vaccine caused poliomyelitis not only in some of those injected but also in associates of those injected. The responsibility for these tragic events, of course, is not that of the authors of this *Report*: they were concerned solely with the evaluation of the vaccine used in the 1954 trial.

It is impossible not to be impressed with the courage of those who undertook a task of this magnitude. The *Report* lists 312 State and Local Health Officials who participated in the field trials in the U. S. and 6 others in Canada and Finland. Listed also are 54 physical therapists, 22 epidemiological intelligence officers, 28 laboratories with their principal scientists, and the 17 members of the Advisory Committee. The latter, incidentally, included three who are listed in the 1954 Di-

* An invited review article on *Evaluation of 1954 Field Trial of Poliomyelitis Vaccine: Summary Report*. Poliomyelitis Vaccine Evaluation Center. University of Michigan, Ann Arbor, Michigan. April 12, 1955. Pp. xiv, 51, Appendix pp. 63. No price.

KA Brownlee. *J Am Stat Assoc*, **50**:1005–1013, 1955.

Thomas Francis, Jr.
1900 - 1969

?

Kenneth A Brownlee
1918 - 1990

An Observed Control Study

- Original design plan: “Observed Control Study”
  - Vaccinate children in the second grade.
  - Controls were first and third graders would not be vaccinated, but observed
  - Biases
    - Not blinded
    - Age differences
- Study was changed in mid stream
  - Children of the first, second, and third grades would be combined.
    - One half would receive vaccine
    - The other matching half, serving as strict controls, would receive a solution of similar appearance.
    - Fewer than half the children were in the second study

Study results

- VE = 62 percent efficacy (lower 5% confidence limit 51) against paralytic polio in the Observed Study Areas
- VE = 72 percent efficacy (lower 5% confidence limit 61) against paralytic polio in the Placebo Study Areas
- Quotes from Brownlee

"To summarize, 59 per cent of the trial was worthless because of the lack of adequate controls. The remaining 41 per cent may be all right but contains internal evidence of bias in favor of the vaccinated. There was hope that an independent trial would be run in Great Britain under the auspices of the Medical Research Council, but this has been abandoned since they concluded that the vaccine was too dangerous."

"It is a pity that explicit credit is not given to whomever was responsible for this change. However, only 41 per cent of the trial was rescued and the remaining 59 per cent blundered along its stupid and futile path."

What we learned from the past

- For vaccine trials, randomization is critical to estimate vaccine efficacy
- For vaccine observational studies there are many factors that need to be dealt with to yield valid and reliable results
  - The unvaccinated comparator group must be selected in a way so that exposure to infection and disease reporting are comparable to those for vaccinated people
  - Given, that the above condition cannot be guaranteed, we may need to adjust for potential confounders and other biases for vaccination and disease outcome
    - Age
    - Prior immunity
    - Health-care seeking behavior
    - Others
  - We will deal with all this in this consultation

Thank you

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