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Article

Polio Eradication or Comeback? Outcome Reporting Bias in the 1954 Poliomyelitis Vaccine Field Trial

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Abstract: Recent wastewater testing suggests the poliovirus is reemerging, raising questions about the efficacy of the current inactivated polio vaccine and mass vaccination to eradicate poliomyelitis. The present study reassessed reported outcomes from the placebo-control study of the 1954 Salk inactivated poliomyelitis vaccine field trial, which studied a population of 1,829,916 U.S. school children from the first three grades. The placebo-control study of the trial reported that the polio vaccine was 80% to 90% effective in reducing cases of laboratory confirmed paralytic poliomyelitis, 60% to 70% effective against type 1 of the virus, and greater than 90% effective against types 2 and 3 of the poliovirus. However, these outcomes are reported as relative risk reductions, and the absolute risk reductions of the 1954 polio vaccine field trial were never reported to the public. The present paper's analysis reveals to the public for the first time that the inactivated poliomyelitis vaccine's absolute risk reduction of laboratory confirmed paralytic poliomyelitis in the placebo-control study is 0.01% to 0.02%, an extraordinarily low clinical effect that impugns the Salk polio vaccine's reported effectiveness. Furthermore, absolute risk reductions for the three poliovirus types are 0.01%, 0.00%, and 0.01%, respectively. Outcome reporting bias in the 1954 inactivated poliomyelitis vaccine field trial casts doubt on eradication of the poliovirus through mass vaccination.

Keywords: polio; paralytic poliomyelitis; Salk vaccine field trial; inactivated polio vaccine; vaccine efficacy; relative risk reduction; absolute risk reduction; number needed to vaccinate; acute flaccid paralysis; polio eradication; mass vaccination

1. Introduction

Considered a "classic of an epidemiologic study of the effectiveness of a vaccine," the 1954 field trial of the Salk inactivated polio vaccine (IPV) for the prevention of paralytic poliomyelitis was considered a great success [1]:

> "The total study population was 1,829,916, consisting of children in the first three grades of school; 749,236 were enrolled in a placebo-control study, and 1,080,680 in an observed-control study. The trial revealed 80 to 90% effectiveness against paralytic poliomyelitis, 60 to 70% against type 1 virus and 90% or more against type 2 and type 3 virus."

However, all was not well in the years following the 1954 field trial. According to a landmark perspective published in the *Journal of the American Medical Association* [2]:

"The disappointment with IPV resulted from the fact that, after a record low of 2,499 cases of paralytic poliomyelitis in 1957, a slight increase was noted in 1958 (to 3,695 cases) and, in 1959, the number of cases more than doubled, to 6,289. As pointed out by Lanmuir [3], 'this rising trend has appeared in spite of the continued use of Salk vaccine which had accumulated to a total of approximately 300 million doses distributed in the United States by the end of 1959. Clearly the control of poliomyelitis is unfinished business.'"

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After distributing doses sufficient to cover more than the entire U.S. population in 1959, an investigation into problems with IPV has never reassessed the vaccine's reported effectiveness in the placebo-control study of the 1954 IPV field trial. Vaccine efficacy in placebo-control trials is calculated as the relative risk reduction (RRR) [4]. However, reported results of clinical trials have often overlooked measures of absolute risk reduction (ARR) and its reciprocal, number needed to treat or vaccinate (NNT or NNV), which provide patients and practitioners with practical information of vaccine efficacy that the RRR lacks [5]. Omitting ARR measures while reporting RRR in a placebo-control trial can be misleading. For example, a 95% RRR does not imply that a vaccine has an ARR of 95% [6].

Following the recent expansion of wastewater surveillance for infectious disease outbreaks [7], the poliovirus has reemerged in Israel, Great Brittan, and the United States, despite the anticipated eradication of polio after decades of mass vaccination [8]. Since 2000, the only vaccine in the United States used against poliomyelitis is the IPV [9]. Yet, once again, concerns about the polio vaccine's effectiveness are rising. To help address these concerns, the present perspective article critically appraised the reported outcomes from the placebo-control study of the 1954 Salk IPV field trial.

2. Method

In the placebo-control study of the 1954 IPV field trial, data were collected from 200,745 children who received the vaccine and 201,229 children who served as controls and did not receive the vaccine. The method for calculating vaccine efficacy from clinical trial data is published elsewhere [4]. A brief summary is presented here. Note that rates may be expressed as decimals or with a percent sign.

- The risk or rate of endpoint events in the experimental or treatment group of a trial is the experimental event rate (EER), and the risk of the events in the placebo or control group is the control event rate (CER).
- The relative risk (RR) is the EER divided by the CER. If the EER and CER have equal values, the RR equals the null value of 1, meaning there is no treatment effect.
- The relative risk reduction (RRR) is 1.00 (or 100%) minus the RR, indicating the strength or distance of the treatment from the null value.
- The absolute risk reduction (ARR) of the treatment effect is the CER minus the EER.
- The number needed to treat or vaccinate (NNT or NNV) to reduce an event is 1 (or 100%) divided by the ARR.

3. Results

Table 1, based on Francis Jr. [10], shows the results of the present analysis. Vaccine efficacy, labelled in Table 1 as the RRR, is shown along with the ARR, 95% confidence intervals, and NNV.

Table 1. 1954 IPV Field Trial—Laboratory Confirmed Cases of Paralytic Poliomyelitis

	Vaccinated (200,745)	Controls (201,229)	RRR	95% CI	ARR	95% CI	NNV
Spinal	8	45	82%	0.62-0.92	0.02%	0.0001-0.0003	5,000
Bulbospinal	2	23	91%	0.63-0.98	0.01%	0.0001-0.0002	10,000
Type 1 Virus Positive	13	39	68%	0.37-0.82	0.01%	0.0001-0.0002	10,000
Type 2 Virus Positive	0	6	100%	-	0.00%	0.0000-0.0000	-
Type 3 Virus Positive	2	25	92%	0.66-0.98	0.01%	0.0001-0.0002	10,000

4. Discussion

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Documentation of the placebo-control study in the 1954 IPV field trial did not explain that vaccine effectiveness was calculated as the relative risk reduction, but the analysis of the present study confirmed that effectiveness values reported in the field study are synonymous with the relative risk reduction, listed under RRR in Table 1. Of relevance, the term vaccine effectiveness as used in the placebo clinical trial of the 1954 field trial is known today as vaccine efficacy, which is measured under strictly controlled conditions [4], providing a much higher standard of evidence than effectiveness measured in uncontrolled observational studies.

In the 1950s, biostatistician Jerome Cornfield explained that relative risk measures are more suitable to appraise "the possible noncausal nature of an agent," such as associations in uncontrolled observational studies, while absolute measures "would be important in appraising the public health significance of an effect known to be causal," such as results in randomized controlled clinical trials [11]. Nevertheless, ignoring Cornfield's explanation of the proper use of relative and absolute measures, randomized controlled clinical trials for vaccines use the relative risk reduction as a measure of vaccine efficacy [4]. Because dividing a number by a fraction results in a higher number, dividing the ARR by the baseline risk or CER results in a higher RRR. As a result, "Clinicians' views of drug therapies are affected by the common use of relative risk reductions in both trial reports and advertisements"[12]. On the other hand, "Describing clinical trial results as absolute risks is the least biased format, for both doctors and patients" [13].

Much of the public may mistakenly assume that vaccine efficacy in a clinical trial indicates the absolute risk reduction, but the true ARR is calculated by subtracting the risk in the vaccine group from the risk in the placebo group. In the 1954 IPV field trial, the relative risk reduction for laboratory confirmed cases of bulbospinal paralytic poliomyelitis is 91%. However, the control group risk is 0.01% and the vaccine group risk is approximately 0.00% for bulbospinal paralytic poliomyelitis, equaling an ARR of barely 0.01%. Furthermore, as listed in Table 1, the number of people who must be vaccinated to reduce one case of laboratory confirmed paralytic poliomyelitis ranges from 5,000 to 10,000 people.

Confusion between the interpretation of the ARR and the RRR in the reporting of the 1954 IPV field trial results has important implications in the public health strategy to eradicate polio through mass vaccination. If IPV efficacy is clinically insignificant, as indicated in the present study findings, what accounts for the widespread drop in polio cases through mass vaccination?

One answer may lie in The World Health Organization (WHO) surveillance strategy for poliomyelitis eradication, in which acute flaccid paralysis (AFP), a polio-like illness, is differentially diagnosed as "confirmed poliomyelitis or non-poliomyelitis AFP" [14]. The WHO surveillance case definition was found to increase sensitivity in detection of AFP "but tends to decrease specificity in detecting paralytic poliomyelitis"[15] , which could explain lower levels of diagnosed paralytic poliomyelitis cases. Unless stools from patients with AFP contain the poliovirus, poliomyelitis is ruled out. The authors also mentioned that "careful assessment of the patient's personal history," including vaccinations, "is crucial in order to narrow the differential diagnosis." Furthermore, according to the American Academy of Pediatrics, "Red flags" for polio in children with acute flaccid limb weakness include "being unvaccinated, undervaccinated or having unknown vaccination status"[16]. These assessments assume that vaccination has a protective effect, but results of the present study suggest such assumptions may be seriously flawed. Further investigations are needed to detect bias in the differential diagnosis of paralytic poliomyelitis and non-poliomyelitis AFP.

5. Conclusion

As polio appears to be making a comeback with the recent expansion of wastewater surveillance, the present study examined the 1954 IPV field trial and found that the vaccine efficacy of the placebo-control trial was affected by outcome reporting bias. Specifi-

cally, the relative risk reduction was reported as the effectiveness of the vaccine, while the absolute risk reduction remained unreported. For the first time, the absolute risk reduction of the 1954 IPV field trial is presented to the public, revealing the extraordinarily low efficacy of the Salk polio vaccine in the placebo-control study. Furthermore, outcome reporting bias in the 1954 IPV field trial casts doubt on the public health strategy to eradicate the poliovirus through mass vaccination.

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