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The first medical meta-analysis: Almroth Wright's 1904 analysis of typhoid vaccine evidence

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Research Article

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Abstract

Objectives

Karl Pearson's 1904 report on antityphoid inoculation is widely regarded as the first medical meta-analysis. However, Pearson analysed rearranged subsets of previously assembled evidence, at the request of one party in a contentious debate, to whom he supplied a satisfactory report, that did not stand up to later scrutiny. This paper compares a modern meta-analysis of Wright's original evidence to Wright's own synthesis, which preceded Pearson's report.

Design:

Historical reanalysis of observational studies.

Setting:

Military, hospital and institutional populations reported in publications from 1899 to 1904.

Participants:

Recipients of antityphoid inoculation and uninoculated members of populations exposed to the same general risk.

Method

Mortality and incidence studies were stratified by inclusion in Pearson's report; case-fatality studies were not stratified. Meta-analyses were performed in Review Manager (RevMan; Cochrane).

Main outcome measures:

Typhoid mortality, incidence of typhoid fever and case fatality among participants who developed typhoid.

Results

Wright estimated reductions of 50–75%; 50% and 52% compared to modern estimates of the pooled odds ratio of 0.31 (95% confidence interval 0.22–0.45; I^2=31.6%); 0.31 (0.18–0.53; I^2=93.6%); and 0.55 (0.45–0.67; I^2=4.0%) in typhoid deaths, incidence, and case fatality rate respectively. The Pearson subset also favoured typhoid vaccination.

Conclusions

Wright's interpretation that antityphoid inoculation was associated with substantial protection, even in those studies selected for Pearson's report, is similar to a modern reanalysis of the data and to modern clinical trials. Wright had assembled, appraised and quantitatively synthesised studies of vaccination before Pearson's reanalysis. Wright's report is a better landmark in the timeline of the development of meta-analysis than Pearson's.

Introduction

Karl Pearson's 1904 report on antityphoid inoculation has acquired a canonical place in the history of research synthesis.[1] His dispute with Almroth Wright is considered as the beginning of evidence-based medicine's triumph over the opinion of experts.[2] Pearson's analysis is described as the first medical meta-analysis.[2–4] Some commentators are more cautious, noting that Pearson knew George Biddell Airy's textbook and placing his work in a longer tradition, from Pascal to Laplace and Gauss, of attempts to combine research data.[3]

Pearson's report was itself a reanalysis. The clinical observations had been assembled and interpreted by Almroth Wright, who had developed a killed typhoid vaccine and advocated its widespread use in the British Army.[5–8] In May 1904, Lieutenant-Colonel R J S Simpson approached Pearson during a contentious debate over antityphoid inoculation. Pearson rearranged the supplied material from Wright's published evidence.[9] He applied a tetrachoric correlation to the data and found the associations low.[1] Pearson's adverse assessment was used in the argument against Wright's case for universal inoculation.[10]

The report was controversial from the outset. Wright did not believe Pearson's conclusion and objected to omissions and additions in the evidence supplied to him. The dispute became public in the BMJ and Lancet: Wright challenged the handling of data, Pearson questioned Wright's statistical competence, and Simpson defended the material he had supplied.[11–13]

Pearson's analysis was subsequently reanalysed. In 1915, Greenwood and Yule's showed that Pearson's correlation coefficient could change with the proportion of a population inoculated even when the underlying fatality rates remained unchanged. Under the assumptions relevant to inoculation studies, they concluded that the coefficient could become "quite meaningless."[14] A century later, Shannon expressed Pearson's tables as odds ratios and showed that a clinically large difference could correspond to a tetrachoric correlation that Pearson described as only moderate.[15]

The current paper looks at the evidence assembled by Wright by applying modern methods of meta-analysis to the field studies.

Wright's synthesis before Pearson

Typhoid was a major cause of illness and death in nineteenth-century armies. The South African War made the problem impossible to ignore: disease killed more British soldiers than enemy action.[16] Wright, then professor of pathology at the Army Medical School at Netley, had developed a killed typhoid vaccine and encouraged voluntary inoculation among soldiers in India and South Africa. He demonstrated to medical officers how to make the vaccine and he encouraged them to record and report its effect.

The evidence was observational. Inoculated soldiers had volunteered for the procedure and could differ from those who declined it in age, rank, or behaviour. Reports came from regiments, hospitals and institutional populations under different conditions. Wright did not ignore these weaknesses. In his 1902 Lancet paper and, more extensively, three papers in The Practitioner in 1904, he discussed inaccurate denominators, uncertain inoculation status, imperfect diagnosis, difficulty constructing comparable control groups and errors arising when figures were collected by many observers in wartime.[5–8] The three Practitioner papers were collected as *A Short Treatise on Anti-Typhoid Inoculation*,

which is more easily accessed today.[9] He warned that systematic error in one direction would not disappear merely because more observations were accumulated.[8]

Wright believed that the reports could be considered collectively. When a narrative approach failed to convince authorities, he assembled relevant field studies, arranged comparable outcomes in synoptic tables and drew quantitative conclusions. He estimated that inoculation was associated with a 50–75% reduction in typhoid deaths, a reduction of at least 50% in incidence, and a 52% reduction in case fatality (8% versus 16.6%).[5–8]

Several elements of modern meta-analysis are therefore recognisable: identification of studies addressing a common clinical question, critical appraisal of their suitability, extraction of comparable outcomes, tabulation of individual results, recognition of differences between studies and quantitative integration into an overall clinical conclusion. Glass would later define meta-analysis as the statistical analysis of results from individual studies for the purpose of integrating their findings.[17] Wright did not statistically weight studies or possess modern methods to quantify heterogeneity or model between-study variation.

Methods

This paper reanalysed the field-trial evidence assembled by Wright. Eligible cohorts compared voluntary recipients of antityphoid inoculation with uninoculated members of populations exposed to the same general risk. Data were extracted from Wright's publications and checked against the original reports.

Three outcomes were examined: mortality from typhoid in the populations studied, incidence of typhoid fever and case fatality among participants who developed typhoid. Mortality and incidence studies were stratified according to whether they were subsequently included in Pearson's 1904 report; case-fatality studies were not stratified because Pearson did not explicitly calculate that statistic.

The original reports cited by Wright were analysed and relevant data extracted. Meta-analyses were performed in Review Manager (RevMan; Cochrane). Effect estimates are presented as odds ratios with 95% confidence intervals. Between-study heterogeneity was expressed using I^2, the proportion of total variation in study estimates attributable to heterogeneity.[18] Random-effects models were used for the analyses.[19]

Results

Table 1 lists the field trials and the sources cited by Wright. For mortality, the pooled OR was 0.31 (95% confidence interval 0.22–0.45; I^2=31.6%). Restricting the analysis to studies included by Pearson gave a similar estimate, OR 0.34 (0.22–0.51) (Fig. 1).

Table 1
Field trials in Wright's antityphoid inoculation synthesis and their original sources

Wright no. †	Abbreviated study name	Study or setting	Population	N	Observation period	Rapporteur	Original report or source cited by Wright
1	Asylum nurses 1897	Barming Asylum nurses and attendants	Hospital staff	200	Oct-Dec 1897	J S Tew; A G R Foulerton; A M Jackson	Public Health, Mar 1898; Lancet, 2 Jun 1900
2*	Army India 1899	British Army in India, 1899	Soldiers	30,353	1899	Official returns	Army Medical Report for 1899
3	15th Hussars 1899	15th Hussars, wives, and officers	Soldiers and families	539	Oct 1899-Oct 1900	Official returns	BMJ and Lancet, 9 Feb 1901; reported by A E Wright
4*	Ladysmith 1900	Garrison of Ladysmith	Soldiers	12,234	Nov 1899-Feb 1900	Official returns	BMJ and Lancet, 14 Jul 1900; reported by A E Wright
5*	Army India 1900	British Army in India, 1900	Soldiers	60,553	1900	Official returns	Army Medical Report for 1900
6	Egypt/Cyprus 1900	British garrison of Egypt and Cyprus	Soldiers	3,389	1900	Principal Medical Officer, Egypt	BMJ and Lancet, 4 May 1901; reported by A E Wright
7*	Tintown H 1901	Tintown Hospital, Ladysmith (patients)	Hospital patients	Not stated	Not stated	D Melville	BMJ, vol I, 1901 (as cited by Wright)
8*	Harrismith H 1902	Stationary Hospital, Harrismith (patients)	Hospital patients	Not stated	Sep 1900-Sep 1901	C Birt	BMJ, 11 Jan 1902
9*	Portland H 1900	Portland Hospital (patients)	Hospital patients	Not stated	1900	H H Tooth	BMJ, 16 Mar 1901
10	Irish Hosp SA 1900	Irish Hospital, South Africa (patients)	Hospital patients	Not stated	1900	J B Coleman	Transactions of the Royal Academy of Medicine in Ireland, vol XIX
11	Scot Red Cross 1900	Scottish National Red Cross Hospital (patients)	Hospital patients	Not stated	1900	Henry Cayley	BMJ, 12 Jan 1901

* Included in Pearson's 1904 report. † Wright's numbering is retained. Study no. 13 was an Army report by Dr R W Dodgson from South Africa that may have been a duplicate and was therefore not included in the present reanalysis. Sensitivity analysis showed that exclusion did not change the results.

Wright no. †	Abbreviated study name	Study or setting	Population	N	Observation period	Rapporteur	Original report or source cited by Wright
12	IYH 1902	Imperial Yeomanry Hospitals (patients)	Hospital patients	Not stated	1900-01	A Elliot; J W Washbourn	Lancet, 18 Jan 1902
14*	Portl'd H staff 1901	Portland Hospital staff	Hospital staff	41	1900	H H Tooth	BMJ, 16 Mar 1901
15*	Deelfontein H 1902	Imperial Yeomanry Hospital, Deelfontein staff	Hospital staff	84	1900-01	A Elliot; J W Washbourn	Lancet, 18 Jan 1902
16*	IYH Pretoria	Imperial Yeomanry Hospital, Pretoria staff	Hospital staff	104	Not stated	R W Dodgson	Official report
17	Bloemfontein H 1900	Nos 8–10 General Hospitals, Bloemfontein staff	Hospital staff	384	1900-01	R W Dodgson	Official report
18*	Red Cross Staff 1900	Scottish Red Cross Hospital staff, second section	Hospital staff	82	1900	Henry Cayley	BMJ, 12 Jan 1901
19*	Manchester Reg 1902	5th Battalion, Manchester Regiment	Soldiers	747	1901-02	J W West	BMJ and Lancet, 5 Apr 1902; reported by A E Wright
20*	City I V 1900	City Imperial Volunteers	Soldiers	1,194	1900	R R Sleman	Privately communicated to Wright
21	Dublin Asylum 1900	Richmond Asylum, Dublin	Asylum population	637	Sep-Dec 1900	H M Cullinan	BMJ, 26 Oct 1901; reported by A E Wright
22	Invalided (1) 1902	Officers invalided from South Africa (first series)	Invalided officers	221	Not stated	A Crombie	Lancet, 3 May 1902
23	Invalided (2) 1902	Officers invalided from South Africa (second series)	Invalided officers	187	Not stated	A Crombie	Lancet, 16 Aug 1902

* Included in Pearson's 1904 report. † Wright's numbering is retained. Study no. 13 was an Army report by Dr R W Dodgson from South Africa that may have been a duplicate and was therefore not included in the present reanalysis. Sensitivity analysis showed that exclusion did not change the results.

Wright no. †	Abbreviated study name	Study or setting	Population	N	Observation period	Rapporteur	Original report or source cited by Wright
24*	7th Hussars 1902	7th Hussars, South Africa	Soldiers	551	Dec 1901-Jun 1902	W A Ward	Official report
25*	Army India 1901	British Army in India, 1901	Soldiers	60,838	Jan-Dec 1901	Official returns	BMJ, 10 Oct 1903
26	Methuen's Col 1900	Lord Methuen's Column, Modder River	Soldiers	13,516	Dec 1899-Mar 1900	Townsend	BMJ, 10 Oct 1903
27	Hosp Natal	No 7 General Hospital, Natal (patients)	Hospital patients	Not stated	Apr-Aug 1900	Watkins-Pitchford	Paper read before the South African Medical Association

* Included in Pearson's 1904 report. † Wright's numbering is retained. Study no. 13 was an Army report by Dr R W Dodgson from South Africa that may have been a duplicate and was therefore not included in the present reanalysis. Sensitivity analysis showed that exclusion did not change the results.

For incidence of typhoid fever, the pooled OR was also 0.31 (0.18–0.53), although heterogeneity was very high (I^2=93.6%). Pearson's subset gave an OR of 0.38 (0.20–0.72); Wright's additional studies gave an OR of 0.17 (0.09–0.35) (Fig. 2).

Among participants who developed typhoid, case fatality was lower after inoculation, with remarkably little heterogeneity between studies (OR 0.55, 0.45–0.67; I^2=4.0%) (Fig. 3).

Discussion

Historical reviews have generally paid less attention to three features of Pearson's report: it was solicited by one party of a contentious policy debate, it analysed a selected part of the evidence assembled by another investigator, and its clinical conclusion proved difficult to sustain. Although Pearson discussed the evidence collectively, he actually analysed five rearranged data sets separately.[1] Shannon calculated the OR for each of these data sets, unlike the pooled analysis of this paper.[15] Nonetheless, the direction and magnitude of vaccination's effect on typhoid incidence and mortality of his calculations concord with the Pearson subset in the current analysis. Both re-analyses of Pearson's data disagree with Pearson's conclusion.

Wright was not a disinterested observer. He had developed the vaccine even though he had disavowed any financial interest; he advocated its adoption and encouraged early users to record and report their experience. His selection and interpretation of the accumulating evidence therefore require the same critical scrutiny as Pearson's subsequent selection. The present reanalysis is restricted by many of the limitations of Wright's analysis. Meta-analysis cannot remove confounding factors or recover observations that were not reported or collected in the original trials.

Modern methods do, however, allow answers that Wright could only address intuitively. Statistical weighting allows individual studies to contribute according to the precision of their information; I^2 quantifies the impact of heterogeneity; and a random-effects model allows the underlying effect to vary between populations.[18,19] Wright's studies show moderate heterogeneity for mortality and high heterogeneity for incidence, but remarkably low

heterogeneity for case fatality. The random-effects model was chosen for this reanalysis in order to reduce the risk of finding a difference that did not exist.

Wright and Pearson agreed on the principal weakness of retrospective evidence. Inoculated and uninoculated men were self-selected populations and could differ in exposure or other characteristics. Pearson proposed registering volunteers and inoculating alternate men.[1,9] Alternate allocation is not randomization in the modern sense, but it belongs in the history of controlled trials. A 1998 meta-analysis of randomized typhoid vaccine trials included almost 1.9 million participants. Three-year cumulative efficacy was 73% (95% CI 65–80%) for two doses of whole-cell vaccine, compared with 51% for Ty21a and 55% for Vi vaccine.[20] Whole-cell vaccines were more reactogenic and their efficacy was strikingly similar to the 50–75% reduction Wright inferred from the field observations of a different era. Wright's vaccine was a progenitor of the whole-cell approach, although later preparations were not identical to his.

Pearson's tetrachoric correlation was mathematically sophisticated but unfamiliar to most physicians. When Wright challenged the report, Pearson dismissed the objections as Wright's failure to understand statistics.[11,12] The vitriol in Wright and Pearson's subsequent medical journal correspondence most likely limited debate for the decade before the First World War. The antivaccination sentiment remained the default. There would be a price to pay.

Several military physicians nevertheless continued work on antityphoid inoculation, particularly William Leishman, who refined vaccine preparation and dosing.[16] The Canadian experience shows how the evidence could lead to a different policy. In the autumn of 1913, Surgeon General Guy Carleton Jones, Director General Medical Services of the Canadian militia, was in England with Canada's powerful Minister of Militia, Sam Hughes. Jones brought Leishman's work to Hughes's attention. Hughes obtained Leishman's temporary services from the War Office, and Leishman visited Canada in early 1914, lecturing in Ottawa, Montreal and Toronto. Adami later wrote that the visit prepared Canada well to accept antityphoid inoculation.[21] Canadian troops were inoculated during mobilization and deployment. The Canadians' low incidence of typhoid throughout the war and reduced case fatality rate (3.7%) were attributed to sanitation and inoculation.[22]

Britain entered the war without comparable universal coverage. Typhoid appeared during the first months of mobilization. Among British troops in the United Kingdom, 262 cases of typhoid and 47 deaths were recorded by 31 January 1915; 237 of those cases and 45 deaths occurred in uninoculated men.[23] The case fatality rate (18%) was similar to that reported by Wright, a decade earlier. Wright renewed his call for universal vaccination. William Osler reminded authorities that typhoid had killed 8022 British soldiers in South Africa and supported Wright's research.[16,24] Kitchener did not make inoculation compulsory, but in late 1914 refusal became incompatible with overseas deployment.[16]

Neither Pearson or Wright sought priority for what would later be termed meta-analysis. For historians, the question is who first treated several clinical investigations as a body of evidence to be critically appraised and quantitatively integrated. Wright initially attempted to win the Army policy argument by encouraging early vaccinators to record and report their findings. When he found that a narrative approach using those reports also failed to convince his opponents, he undertook the first meta-analysis. He assembled the studies, assessed their limitations, organised comparable outcomes and calculated the treatment effect from proportions. Wright believed the effect was obvious. Such was the impact of his argument, that his opponents asked Pearson to reconsider a subset of the same material. Greenwood and Yule's caution remains useful a century later: mathematical complexity should not be confused with evidential validity. Statistical methods earn their authority by clarifying evidence, not by making a conclusion inaccessible to clinical scrutiny.[14] Wright's 1904 synthesis in The Practitioner therefore has a stronger claim than Pearson's subsequent reanalysis to be included in the timeline of meta-analysis development.

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Figures

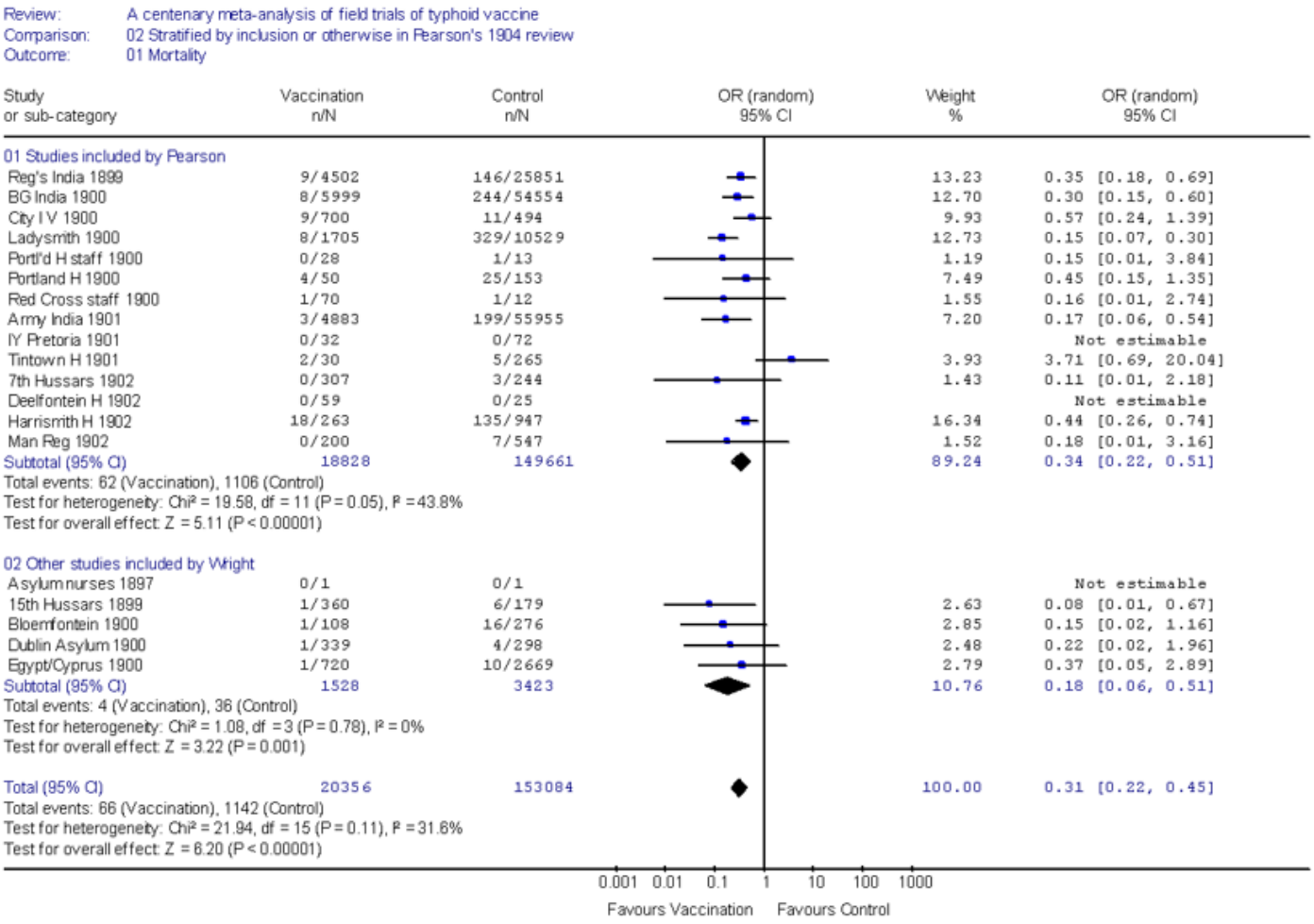


Figure 1

Effect of typhoid vaccination in Wright's field trials: mortality. Studies are stratified by inclusion in Pearson's 1904 review.

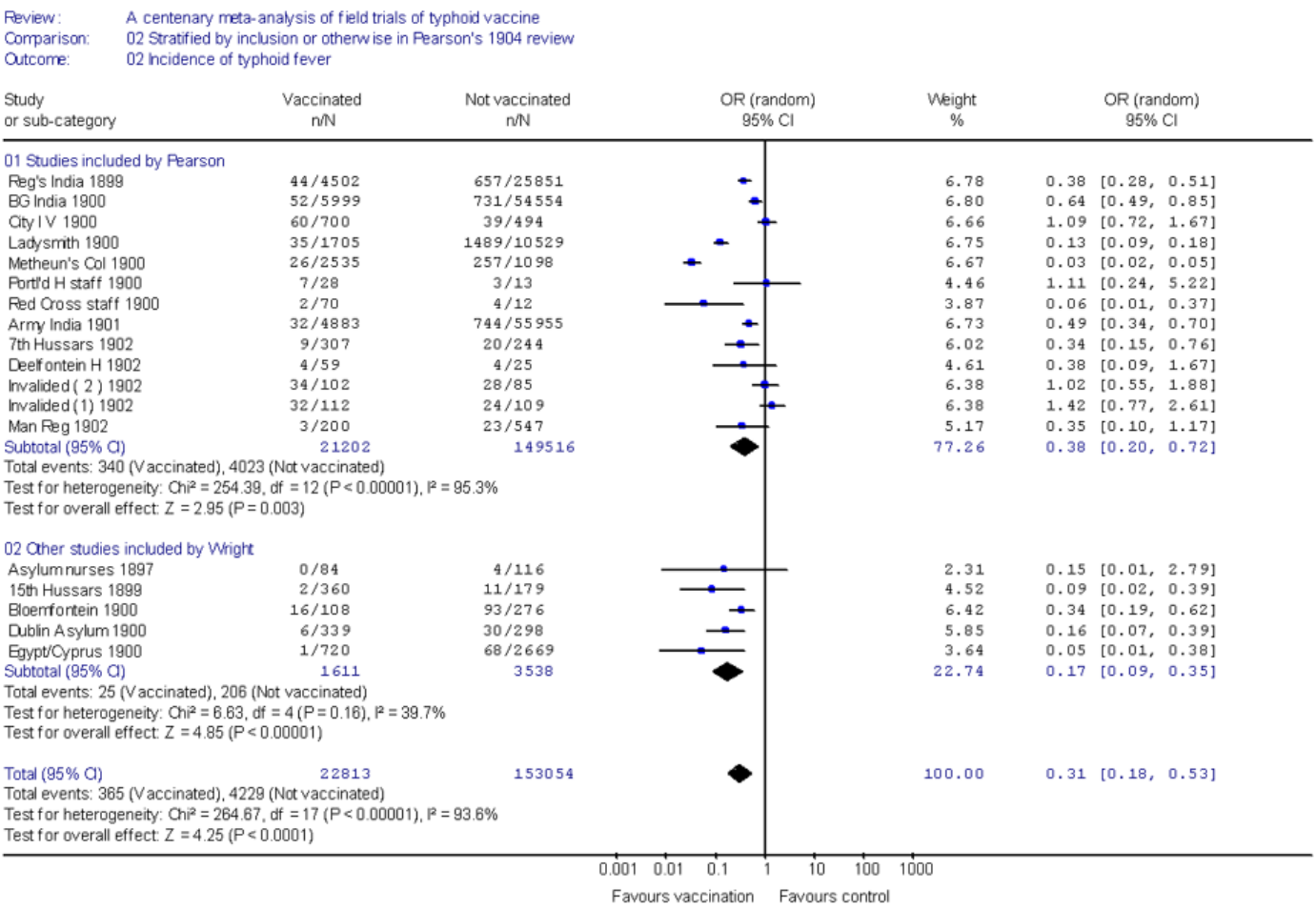


Figure 2

Effect of typhoid vaccination in Wright's field trials: incidence of typhoid fever. tudies are stratified by inclusion in Pearson's 1904 review.

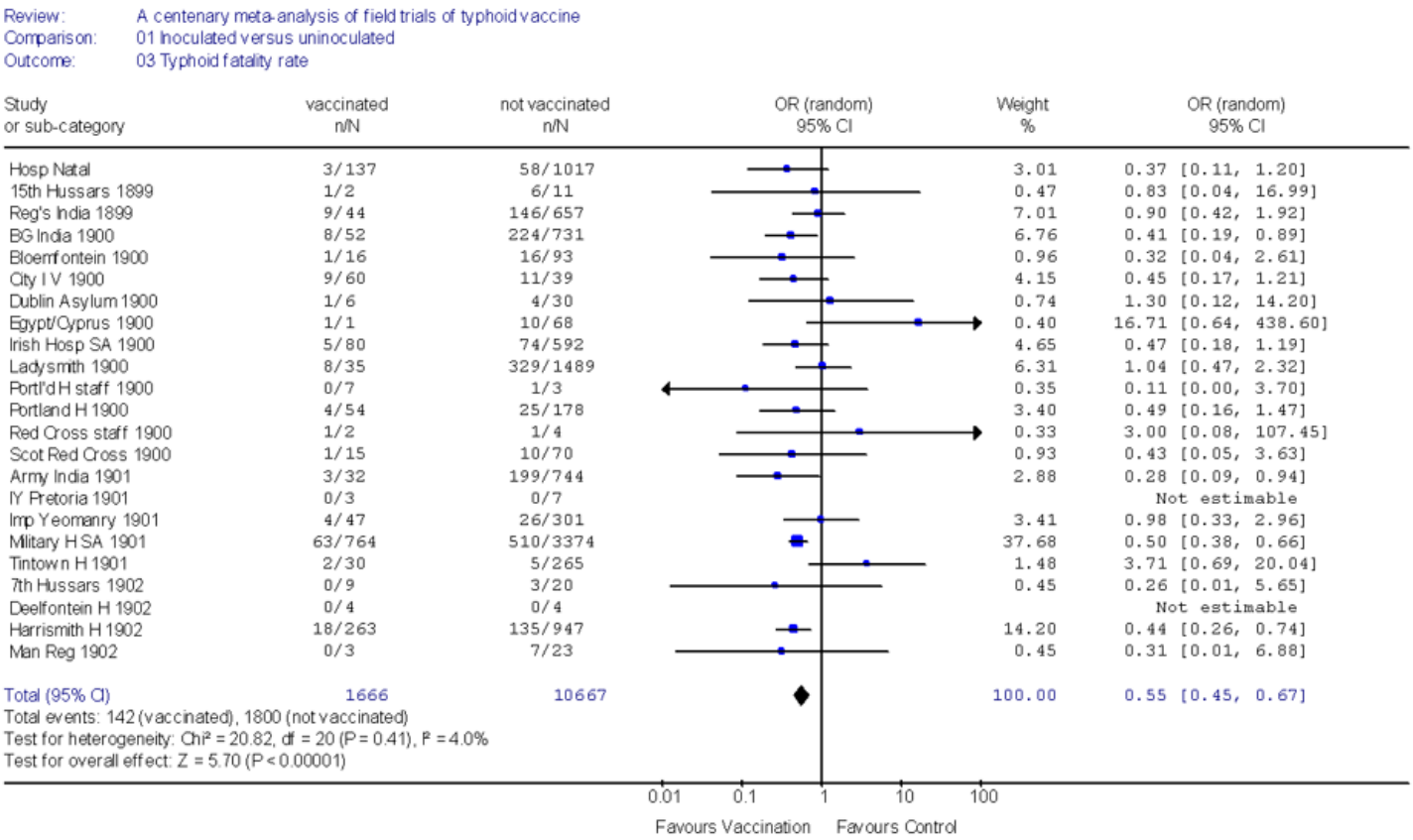


Figure 3

Effect of typhoid vaccination in Wright's field trials: typhoid case fatality.