

VACCINES FOR PREVENTING TYPHOID FEVER

Engels EA, Lau J

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ABSTRACT

Background

Whole cell vaccines, consisting of relatively crude preparations of *Salmonella typhi* administered parenterally, are effective but have a high incidence of adverse effects. Two vaccines have been developed more recently. Ty21a (an attenuated strain of *S. typhi* administered orally) and Vi (the purified bacterial capsule, given parenterally), have appeared less toxic than the older whole cell vaccines and are thought to be equally effective.

Objectives

The objective of this review was to assess the effects of typhoid fever vaccines.

Search Strategy

We searched the Cochrane Library, Medline, Index Medicus, Embase and reference lists of articles.

Selection Criteria

Randomised trials comparing typhoid vaccines to other types of vaccine or placebo.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data.

Main Results

Seventeen studies, involving nearly two million people, were included. For the whole cell vaccines single dose regimens provided significant protection for the first two years. Two dose regimens provided significant protection for five years. For the Ty21a vaccine, both two and three dose regimens provided statistically significant protection for two years. The three dose regimen provided protection in the third and fourth years, but protection was not statistically significant in the fifth year. The Vi vaccine provided protection for two years, but the protection in the third year was not significant. The three year cumulative efficacy of two doses of whole cell vaccines was 73% (95% confidence interval 65-80), three doses of Ty21a was 51%, (95% confidence interval 35 to 63) and one dose of Vi was 55% (95% confidence interval 30 to 71). Data on adverse effects were limited, but indicate that whole cell vaccines are more toxic than the newer Ty21a and Vi vaccines.

Reviewers' conclusions

The whole cell vaccines provided more prolonged protection than either the Ty21a vaccine or the Vi vaccine. However whole cell vaccines are associated with higher toxicity.

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BACKGROUND

Typhoid fever continues to be a substantial public health problem in developing countries. Each year, 33 million people become ill and over 500,000 people die from this infection. [Inst Medicine 1986] Typhoid is rare in

industrialized nations, though travelers to endemic countries may occasionally acquire the disease. [Bennish 1995]

There is longstanding interest in the use of vaccines to prevent this disease. In 1904 the statistician Karl Pearson, in what may have been the first published meta-analysis on any topic, reviewed seven studies of a heat-inactivated typhoid vaccine conducted in British Army units. [Pearson 1904] He concluded that these vaccine studies were flawed and that taken together they failed to demonstrate the efficacy of this vaccine. Despite Pearson's assessment and concerns about toxicity, this vaccine was later routinely used in the British Army.

Since the first report of a randomized controlled trial of a typhoid vaccine in 1962, [Yug Ty Comm 1962] the results of at least 29 other trials have been published. Whole cell vaccines, consisting of relatively crude preparations of *Salmonella typhi* administered parenterally, were found to be effective but to have a high incidence of side effects. [Ashcroft 1967, Yug Typhoid Comm 1964] Two vaccines developed more recently, Ty21a (an attenuated strain of *S. typhi* administered orally) and Vi (the purified bacterial capsule, given parenterally), have appeared less toxic than the older whole cell vaccines and are thought to be equally effective. [Bennish 1995]

Whether any of the available vaccines would be useful in typhoid prevention in the developing world remains uncertain. [Lancet 1992] None of the efficacy trials directly compared the newer vaccines with each other or with the whole cell vaccines. Furthermore, studies have provided widely varying estimates of efficacy and toxicity, leaving the true benefits of vaccination uncertain. Important factors that might influence the efficacy of the vaccines, such as age of vaccinees and their risk of acquiring typhoid fever, have not been systematically assessed.

In industrialized countries, physicians may be called upon to advise travelers on their risk for acquiring typhoid and ways to reduce that risk. Indeed, though typhoid vaccines were initially evaluated in populations living in endemic regions, today their major use is for travelers, and one third of travelers presenting to physicians for advice receive vaccination. [Behrens 1994] Most are unlikely to develop typhoid; those at highest risk include travelers making prolonged visits to remote areas of endemic nations. [Bennish 1995]

A clearer understanding of typhoid vaccine efficacy and toxicity would be useful for physicians in both developing and developed nations. We therefore conducted a systematic review, the first since Pearson's review in 1904 and the first to include randomized controlled trials, to evaluate published data on these vaccines.

The full text for this review has been published as a meta-analysis in the British Medical Journal. [Engels 1998]

OBJECTIVES

To estimate the efficacy of currently available typhoid vaccines.

To estimate the toxicity of currently available typhoid vaccines.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

1. To be included in this analysis, a study had to be a randomized field trial that reported the number of cases of typhoid fever in each trial arm.
2. Included trials had control arms in which subjects received either placebo or a vaccine against a disease other than typhoid fever.
3. Included trials studied vaccines in one of 3 currently available classes: the Ty21a vaccine; the Vi vaccine; and the whole cell vaccines, inactivated with alcohol, formol, acetone, or heat (the heat-inactivated vaccine is the only vaccine in this class currently widely available).

Types of participants

Any individual participating in a randomized field trial of a typhoid vaccine. Trial participants are described further in the Table of included studies.

Types of intervention

Vaccination with typhoid fever vaccine or inactive agent (placebo or vaccine for a disease other than typhoid fever).

Number of doses varied for the different vaccine types: 1-3 doses for Ty21a, 1 dose for Vi, and 1-2 doses for whole cell vaccines.

Types of outcome measures

Outcomes were documented cases of typhoid fever in each year of follow up.

In all trials the primary means of diagnosing cases of typhoid was isolation of *S. typhi* from cultured blood, but 5 trials also included cases documented by stool, urine, or duodenal fluid cultures. [Tapa 1975, Polish Ty Com 1966, Levine 1987, Levine 1990, Ashcroft 1967]

Efficacy data were reported by trials on either an "any-dose" basis (data available for subjects getting at least one vaccine dose) or an "all-dose" basis (data available only for subjects getting all assigned vaccine doses).

Outcomes for toxicity included fever, swelling at injection site (for injectible whole cell and Vi vaccines), vomiting (for oral Ty21a), diarrhea (for Ty21a), and missed school or work. Definitions of each of these outcomes were those provided in the individual trials.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: [Cochrane Infectious Diseases Group](#) search strategy

To identify published efficacy trials of typhoid vaccines, we conducted a literature search of the MEDLINE database from 1966 through 1996. We also conducted searches of Index Medicus (1955-66), EMBASE, and the Cochrane Library database. We obtained additional studies from reference lists of retrieved articles and included studies in any language.

In the database searches we used the textwords: Salmonella, salmonellosis, typhoid, and vaccine.

METHODS OF THE REVIEW**Data extraction**

From each trial report we extracted: vaccine formulation and number of doses, duration of follow-up, number of subjects, number of typhoid fever cases, and number of individuals with side effects.

We noted whether randomization was adequately described (description of unit of randomization and method of generating random assignment). We also recorded whether treatment assignment was concealed from investigators (either stated explicitly or implied by a description of vaccine coding); whether diagnosis of typhoid fever occurred blinded to assignment; whether surveillance for cases was active (personnel going into the field to identify cases), intermediate (relying on pre-existing clinics, encouraged to evaluate patients for typhoid), or passive (relying on reporting of cases by others, without efforts to increase surveillance); and whether efficacy could be calculated on an "any-dose" basis (data available for subjects getting at least one vaccine dose) or an "all-dose" basis (data available only for subjects getting all assigned vaccine doses). These data on methodological quality are presented in the Tables of included studies, and in our published meta-analysis. [Engels 1998] Two of the authors independently extracted these data; discrepancies were resolved through consensus discussions.

Studies presented data from several vaccine arms, each compared with the single inactive arm. In the Data

Tables, and corresponding reference sections, these trial arms are identified separately by letter, to allow their results to be examined separately by the reader. For example, data for the Ashcroft heat-inactivated vaccine are presented as "Ashcroft 1967 A," while data for the Ashcroft acetone-inactivated vaccine are presented as "Ashcroft 1967 B."

Analysis of vaccine efficacy

Published trials provided efficacy data for regimens with different numbers of doses and after various durations of follow-up. We examined efficacy separately for various numbers of doses and in different years of follow-up, by only including relevant subject experience from each trial. When trials included followup for only part of a year, we rounded to the nearest year to decide for which year's estimate to use the data.

In the Data Tables we report for each arm the number of individuals with documented typhoid fever and the number of individuals followed in that arm. This allows calculation of Peto odds ratios. A more valid approach to these data would take into account the fact that some trials followed individuals for slightly more or less than 1 year; this approach, taken in our published meta-analysis, [Engels 1998] calculates the number of person-years of observation for each trial arm. From those data, one can calculate incidence rates and their ratios for each trial intervention arm, and then one can calculate a random effects pooled incidence rate ratio. [Engels 1998, Ioannidis 1995] The Peto odds ratio, presented in this Cochrane review, may approximate the pooled incidence rate ratio, since incidence rates were low and data were available for whole years of many included trials.

Efficacy of the vaccines is defined as 1-(pooled incidence rate ratio), or to an approximation, 1-(Peto odds ratio). Efficacy is expressed as a percentage.

When studies compared several vaccine arms to a single control arm, we included control subjects several times in the Data Tables (once for each comparison of a typhoid vaccine and the control regimen). This analysis therefore overcounted some of the control subjects. To evaluate the effect of this overcounting of control subjects, in a separate sensitivity analysis we divided the control groups into smaller groups for each of the comparisons to typhoid vaccine arms; when we pooled these estimates of vaccine efficacy, the pooled estimates were similar to those from our primary analyses. [Engels 1998] Also, some of the data for 1 dose of whole cell vaccines come from subjects randomized to, but not completing, 2-dose regimens.

Some of the trials included in this review do not report year-specific efficacy. These studies report cumulative efficacy over several years, but these data are not useful for calculating year-specific data. The data from these studies and others in this review are used to estimate cumulative 3-year efficacy for typhoid vaccines. The Data Tables and Analysis sections present data needed for the Peto odds ratio over 3-years (specifically the number of cases of typhoid over 3 years and number of individuals followed in each trial), and our previously published meta-analysis presents results for the incidence rate ratios cumulative over 3 years. [Engels 1998]

Analysis of vaccine toxicity

Some field studies reported data on side effects following vaccination. These toxicity data from the large field trials were used only if investigators actively sought out the occurrence of side effects; in general, investigators only attempted this active surveillance for subsets of the trial arms.

Side effects examined included fever, swelling at injection site (for Vi and whole cell vaccines), vomiting (for Ty21a only), diarrhea (for Ty21a only), and missed school or work. We used the definitions of these outcomes that were provided by the individual reports. When the occurrence of side effects was reported after each of several doses, we report only the occurrence after the first dose. Similarly, when reports provided estimates of the incidence of adverse events for different time points following vaccination, we present data corresponding to 24 hours after vaccination.

DESCRIPTION OF STUDIES

Characteristics of included studies are described under "Table of included studies."

METHODOLOGICAL QUALITY

The 7 trials of the Ty21a and Vi vaccines used either active or intermediate-level surveillance for efficacy, whereas the 10 trials of the whole cell vaccines used passive surveillance for efficacy (3 trials) or did not describe the mode of surveillance (7 trials).

All of the trial reports described concealment of assignment status or, by describing a system of coded vaccines, implied that assignment had been concealed. However, only 8 of the 17 trial reports described both randomization and blinding. Only 3 of 13 trials examining multi-dose regimens reported data on an "any-dose" basis. Data for each trial are included in the published meta-analysis. [Engels 1998]

Only 7 trials of whole cell vaccines, 2 trials of Ty21a vaccine, and 1 trial of Vi vaccine reported data on toxicity derived from active surveillance.

RESULTS

The 17 trials in this review included 1,866,951 subjects. The following trials provided efficacy data for individual years of follow-up, or for follow-up cumulative to 3 years:

5 trials of Ty21a (326,689 subjects, 11 vaccine arms)
[Wahdan 1982, Levine 1987, Levine 1990, Simanjuntak 1991, Black 1990]

2 trials of Vi (17,822 subjects, 2 vaccine arms)
[Klugman 1996, Acharya 1987]

10 trials of whole cell vaccines (1,522,440 subjects, 21 vaccine arms)
[Yug Ty Comm 1962, Yug Ty Comm 1964, Hejfec USSR 3 1965, Hejfec USSR 4 1965, Hejfec USSR 5 1966, Polish Ty Com 1966, Ashcroft 1967, Hejfec 1968, Hejfec 1969, Tapa 1975]

Vaccine Efficacy

Efficacy data for specific years of follow-up and for varying numbers of doses are provided in Data Tables. Some estimates for Ty21a and Vi vaccine regimens were based on few study arms or subjects.

The Peto odds ratios displayed in the Analysis section do not agree exactly with the results we published previously. [Engels 1998] There are at least 2 reasons to prefer our previous analysis, in which we pooled incidence rate ratios using a random effects model. First, the odds ratio and its confidence interval only approximate the incidence rate ratio and confidence interval, which is the more appropriate measure for these data. Second, a random effects model is more appropriate than a fixed effects model with these data, since heterogeneity is present. Therefore, we provide in this section a table from our previously published work with the efficacy of the typhoid fever vaccines (efficacy = 1 minus (random effects pooled incidence rate ratio))

Efficacy data (from [Engels 1998])--Percent efficacy (95% CI), by Year and Number of Doses

Ty21a--one dose
Yr 1 25 (-9 to 49)
Yr 2 35 (-8 to 61)
Yr 3 1 (-87 to 48)
Yr 4 -6 (-77 to 37)
Yr 5 -10 (-113 to 43)

Ty21a--two doses
Yr 1 52 (24-69)
Yr 2 71 (44-85)
Yr 3 22 (-54 to 60)
Yr 4 19 (-41 to 53)

Yr 5 7 (-84 to 53)

Ty21a--three doses

Yr 1 50 (18-69)

Yr 2 60 (44-71)

Yr 3 60 (35-76)

Yr 4 78 (35-93)

Yr 5 47 (-24 to 78)

Vi--one dose

Yr 1 67 (44-81)

Yr 2 52 (4-76)

Yr 3 50 (-11 to 78)

Yr 4 No data

Yr 5 No data

Whole cell vaccine--one dose

Yr 1 65 (49-76)

Yr 2 51 (6-74)

Yr 3 71 (-5 to 92)

Yr 4 37 (-98 to 80)

Yr 5 79 (44-92)

Whole cell vaccine--two doses

Yr 1 74 (62-82)

Yr 2 72 (56-82)

Yr 3 74 (50-87)

Yr 4 73 (42-87)

Yr 5 67 (43-80)

As can be seen from these pooled efficacy estimates, for the whole cell vaccines, 1-dose regimens provided significant protection in each of the first 2 years, and 2-dose regimens provided significant protection in each of the first 5 years. Protection provided by 2-dose regimens was not statistically significant in the sixth and seventh years.[Yug Ty Comm 1962, Ashcroft 1967, Tapa 1975]

For the Ty21a vaccine, both 2- and 3-dose regimens provided statistically significant protection in each of the first 2 years. The 3-dose regimen provided protection in the third and fourth years, but protection was not statistically significant in the fifth year. Data for efficacy of 3 doses of the Ty21a vaccine in the fourth and fifth years were from 2 reports that presented extended follow-up data for a single arm of a 4-arm trial;[Levine 1987] this arm had shown the greatest efficacy at the end of the first 3 years, but no follow-up data were presented for the 3 less effective arms.

The Vi vaccine provided protection in each of the first 2 years after vaccination. The protection in the third year (50%) was similar to that in the second year (52%), but the protection in the third year was not significant. There were no published efficacy data beyond 3 years of follow-up.

The Data Tables and Analysis sections also describe pooled estimates of 3-year cumulative efficacy. These odds ratio estimates approximate the corresponding incidence rate ratios. The 3-year cumulative efficacy estimates we previously derived are presented below.

Three-cumulative efficacy data based on incidence rate ratios over three years (from Engels 1998)--Percent efficacy (95% CI)

Whole cell vaccines, 2 doses: 73 (65-80)

Ty21a vaccine, 3 doses: 51 (35-63)

Vi vaccine, 1 dose: 55 (30-71)

Vaccine Toxicity

Only 10 trials reported data on side effects of vaccination. Whole cell vaccines appeared to be associated with side effects more often than comparison arm regimens, though substantial heterogeneity was present. Based on limited data, Vi vaccine appeared less toxic than a comparison vaccine (meningococcal vaccine), while Ty21a appeared to be associated with fever and vomiting more often than placebo.

Toxicity data, presented in Data Tables and Analyses, are difficult to interpret for at least 2 reasons. First, the non-typhoid vaccines in the comparison arms varied (see Table of Included Studies), both within the class of whole cell vaccines and between this class and the other typhoid vaccines. While this is acceptable when interpreting efficacy data, since none of the comparison vaccines is expected to protect against typhoid fever, this situation greatly complicates examination of side effect data. This likely explains some of the heterogeneity of odds ratios for side effects among whole cell vaccine trials. Second, these large field trials were primarily designed to evaluate vaccine efficacy, and surveillance for and reporting of toxicity outcomes are limited.

DISCUSSION

In this review the 73% three-year efficacy of the whole cell vaccines exceeded the 51% efficacy of the Ty21a vaccine. Although individual trial estimates varied widely for two doses of the inactivated whole cell vaccines (36-94%) and three doses of Ty21a (19-96%), the pooled estimates from this study were associated with much narrower confidence intervals. The 55% efficacy estimate for the Vi vaccine, though imprecise, is similar to the estimate for the Ty21a vaccine.

In the absence of trials directly comparing typhoid vaccines, the present analysis of controlled trials provides the most valid means of assessing these vaccines, and it delineates the efficacy of these vaccines more precisely than previous qualitative reviews, which have tended to equate their efficacy. [Bennish 1995, ACIP 1994] The whole cell vaccines provided more prolonged protection than either the Ty21a vaccine or the Vi vaccine. When each year of follow-up was examined separately, the whole cell vaccines provided statistically significant protection for 5 years, Ty21a for 4 years, and Vi for 2 years. Immunization with fewer doses of the whole cell and Ty21a vaccines did not provide protection as sustained as regimens with standard numbers of doses.

The data presented by these large field trials support a general clinical impression that whole cell vaccines have more side effects than the newer Ty21a and Vi vaccines. It must be noted, however, that these trials may not be the best source of data to assess toxicity due to typhoid vaccination, because they were large scale trials designed to assess efficacy, and the reports provide little information on secondary endpoints. Also, because comparison arm vaccines varied among the field trials, odds ratios for side effects have unclear meaning.

Data from other sources confirm the relatively high toxicity of whole cell vaccines. In our previous meta-analysis, we calculated average rates of developing side effects from typhoid vaccination, based on data from randomized trials and uncontrolled case series. [Engels 1998] Fever occurred more often after administration of heat-inactivated vaccine (15.7%, 95% confidence interval 11.5-21.2%) than Ty21a (2.0%, 0.7-5.3%) or Vi (1.1%, 0.1-12.3%). Swelling at the injection site also occurred more often with the heat-inactivated vaccine (20.0%, 12.9-29.7%) than with Vi (3.7%, 1.3-9.6%). Ty21a was associated with a 2.1% incidence of vomiting (0.6-7.8%) and a 5.1% incidence of diarrhea (1.7-14.5%). Ten percent of subjects missed school or work after receiving the heat-inactivated vaccine; only 1 study of the newer vaccines specifically commented on this outcome (0% in a study of Vi). The superior efficacy of the whole cell vaccines must therefore be weighed against their higher incidence of adverse events.

Whether a routine vaccination program using any of these moderately effective vaccines would be useful in reducing the incidence of typhoid in developing countries, where attack rates may approximate 1% per year, is a complex issue. The effectiveness of these vaccines in actual public health practice will be different than the efficacy noted in field trials, since the result of a vaccination program depends on additional factors that influence population-level immunity ("herd immunity"). These factors include the demographic distribution of susceptible and immune individuals in the population, the number of secondary cases that arise from each primary case, the degree of vaccination coverage achieved, and the duration of natural and vaccine-associated immunity.

Herd immunity may play a role in the epidemiology of typhoid fever. A typhoid control program in Thailand, based in part on use of a heat-inactivated vaccine, resulted in a 10-fold decrease in rates of disease over 8 years in all examined age groups, despite vaccination only of school age children. [Bodhidatta 1987] The number of cases of

paratyphoid fever remained unchanged, suggesting that the wide-based decrease in cases of typhoid could be attributed to immunization and herd immunity and not to general improvements in sanitation. Similarly, decreases in typhoid cases were noted among an unvaccinated population at the onset of Ty21a vaccine trials in neighboring areas. [Levine 1989]

The relatively precise estimates of efficacy and toxicity that this study provides can be used to model the potential impact of a vaccination program in typhoid-endemic nations. We did not find a relationship between vaccine efficacy and either an individual's risk of disease, as reflected by control rates varying from 6 to 810 cases per 100,000 persons per year, or age, though we were limited by incomplete reporting of age-specific data. [Engels 1998] Because the whole cell vaccines provide the greatest protection for the longest duration, these vaccines may be best suited among available vaccines for control programs. However, the substantial toxicity of the whole cell vaccines must be taken into careful account. The decision regarding which vaccine, if any, would be appropriate for typhoid control in endemic nations depends, in the final analysis, on a careful weighing of the benefits of vaccination with side effects and costs. Currently none of the typhoid vaccines is administered as part of the World Health Organization's Expanded Programme on Immunization, which targets children less than one year of age.

The conclusions of this review should also be interpreted in the context of variations in dose and formulation of Ty21a. Whereas Ty21a is available in most countries as a 3-dose regimen of enteric-coated capsules, it is licensed for administration to travelers in the United States and Canada as a 4-dose series. A 3-year Chilean trial reported that 4 doses of the Ty21a vaccine is 40% more effective than 3 doses; [Ferrecchio 1989] we did not include this study in our systematic review because it lacked a suitable control arm. Furthermore, our analysis suggests that the liquid formulation of Ty21a may be more effective than the enteric capsule formulation (Data Tables and [Engels 1998]); this liquid formulation is only now becoming commercially available. There are no published data examining whether 4 doses of any formulation of Ty21a provides protection for longer than 3 years.

For travelers to typhoid-endemic countries, further research is needed to determine the efficacy of these vaccines. Though their overall incidence of disease is low (less than 20 per 100,000 travelers to endemic countries), higher-risk travelers comprise an important target group for typhoid vaccines. None of the trials included in this report studied this population, and it is not clear that efficacy for travelers can be extrapolated from efficacy of vaccines in endemic countries, where individuals may already have some baseline immunity due to inapparent infections. [Joo 1979] A single case-control study of travelers to India estimated the efficacy of the Ty21a vaccine to be 23%, [Hirschel 1985] considerably lower than our estimate for populations living in typhoid-endemic countries.

The present study demonstrates that the whole cell vaccines are more effective than either the Ty21a or Vi vaccines. Whether the higher toxicity of whole cell vaccines outweighs their added efficacy will likely depend on the setting in which vaccination is administered. In the absence of direct comparison trials, the present analysis provides useful data for comparing these vaccines.

REVIEWER'S CONCLUSIONS

Implications for practice

A tentative application of results from this review suggests that vaccination with Vi may be an appropriate choice for short-term travelers. For many travelers protection need not be prolonged, and this vaccine compares favorably with the whole cell vaccines in efficacy during the first year following vaccination. Also, the Vi vaccine has less toxicity than the whole cell vaccines. Similarly, 4 doses of Ty21a may be effective prophylaxis for travelers. Though typhoid vaccination of travelers may not be cost-effective, [Behrens 1994] individual travelers may still opt for vaccination after discussing with their physicians the benefits and side effects of prophylaxis, and our study provides useful data on which to base this discussion.

Because the whole cell vaccines provide the greatest protection for the longest duration, these vaccines may be best suited among available vaccines for public health programs in the developing world. However, the substantial toxicity of the whole cell vaccines must be taken into careful account. The decision regarding which vaccine, if any, would be appropriate for typhoid control in endemic nations depends, in the final analysis, on a careful weighing of the benefits of vaccination with side effects and costs.

Implications for research

The apparent efficacy of an intervention may vary with differences in trial design. [SORT 1994] Only 8 of the 17 efficacy trials provided descriptions of both randomization methods and blinding of treatment assignment during follow-up. Because there were few trials in each vaccine class, we were unable to analyze the effect of differences in study design on reported efficacy. These inconsistencies in study design and reporting highlight the need for better international cooperation for trials of vaccines that have potential importance for public health. [CONSORT 1996]

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POTENTIAL CONFLICT OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

TABLES**Characteristics of included studies**

Study	Acharya 1987
Methods	Active surveillance Followup 1.4 yrs
Participants	Age 5-44 yrs Nepal
Interventions	Vi vaccine, vs. pneumococcal vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	A
Study	Ashcroft A 1967
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 7 yrs
Participants	Ages 5-15 yrs Guyana
Interventions	Inactivated vaccine (heat) vs. tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Data for efficacy of 1 dose are derived from subjects randomized to, but failing to

	complete, 2-dose regimen.
Allocation concealment	A
Study	Ashcroft B 1967
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 7 yrs
Participants	Ages 5-15 yrs Guyana
Interventions	Inactivated vaccine (acetone) vs tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Data for efficacy of 1 dose are derived from subjects randomized to, but failing to complete, 2-dose regimen.
Allocation concealment	A
Study	Black 1990 A
Methods	Intermediate surveillance Randomization by classroom Followup 5 yrs
Participants	Ages 5-22 yrs Chile
Interventions	Ty21a enteric capsules, vs. placebo 2 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood or bone marrow
Notes	
Allocation concealment	A
Study	Black 1990 B
Methods	Intermediate surveillance Randomization by classroom Followup 5 yrs
Participants	Ages 5-22 yrs. Chile
Interventions	Ty21a enteric capsules, vs. placebo 1 dose
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood or bone marrow
Notes	
Allocation concealment	A
Study	Hejfec 1968 A
Methods	Surveillance method not described Followup 2.5 yrs
Participants	Ages 7-16 yrs USSR
Interventions	Inactivated vaccine (heat, first formulation) vs. paratyphoid vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>

Notes	Trial studied 2 separate formulations of heat-inactivated vaccine
Allocation concealment	A
Study	Hejfec 1968 B
Methods	Surveillance method not described Followup 2.5 yrs
Participants	Ages 7-16 yrs USSR
Interventions	Inactivated vaccine (heat, second formulation) vs. paratyphoid vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial studied 2 separate formulations of heat-inactivated vaccine
Allocation concealment	A
Study	Hejfec 1969 A
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 1.8 yrs
Participants	Ages 7-20 yrs USSR
Interventions	Inactivated vaccine (heat) vs. paratyphoid vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	B
Study	Hejfec 1969 B
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 1.8 yrs
Participants	Ages 7-20 yrs USSR
Interventions	Inactivated vaccine (acetone) vs. paratyphoid vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	B
Study	Hejfec USSR 3 1965
Methods	Surveillance method not described Followup 0.7 yrs
Participants	Ages 7 to ? yrs USSR
Interventions	Inactivated vaccine (alcohol) vs. tetanus toxoid 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial also studied a "chemical"-processed subunit vaccine, which was not extracted

	for this review
Allocation concealment	A
Study	Hejfec USSR 4 1966 A
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 7 to 18 yrs USSR
Interventions	Inactivated vaccine (heat) vs. tetanus toxoid 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial also studied a "chemical"-processed subunit vaccine, which was not extracted for this review
Allocation concealment	A
Study	Hejfec USSR 4 1966 B
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 7-18 yrs USSR
Interventions	Inactivated vaccine (alcohol) vs. tetanus toxoid vaccine 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial also studied a "chemical"-processed subunit vaccine, which was not extracted for this review
Allocation concealment	A
Study	Hejfec USSR 5 1966 A
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 7 to ? yrs USSR
Interventions	Inactivated vaccine (heat vaccine, first formulation) vs. tetanus toxoid vaccine 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial also studied 3 "chemical"-processed subunit vaccines, which were not extracted for this review
Allocation concealment	A
Study	Hejfec USSR 5 1966 B
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 7 to ? yrs USSR

Interventions	Inactivated vaccine (heat, second formulation) vs. tetanus toxoid vaccine 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
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Interventions	Inactivated vaccine (alcohol) vs. tetanus toxoid
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	Trial also studied 3 "chemical"-processed subunit vaccines, which were not extracted for this review
Allocation concealment	A
Study	Klugman 1996
Methods	Active surveillance for efficacy Active surveillance for toxicity Followup 3 yrs
Participants	Age 5-16 yrs South Africa
Interventions	Vi vaccine, vs. meningococcal vaccine 1 dose
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	A
Study	Levine 1987 A
Methods	Intermediate surveillance Randomization by classroom Followup 3 yrs
Participants	Ages 6-21 yrs Chile
Interventions	Ty21a vaccines: doses of enteric capsules given 21 days apart, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	One active arm of multi-arm study
Allocation concealment	A
Study	Levine 1987 B
Methods	Intermediate surveillance Randomization by classroom Published followup 5 yrs only for this arm

Participants	Ages 6-21 yrs Chile
Interventions	Ty21a vaccines: doses of enteric capsules given 2 days apart, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	One active arm of multi-arm study
Allocation concealment	A
Study	Levine 1987 C
Methods	Intermediate surveillance Randomization by classroom Followup 3 yrs
Participants	Ages 6-21 yrs. Chile
Interventions	Ty21a vaccine: doses of gelatin capsules given 21 days apart, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	One active arm of multi-arm study
Allocation concealment	A
Study	Levine 1987 D
Methods	Intermediate surveillance Randomization by classroom Followup 3 yrs
Participants	Ages 6-21 yrs. Chile
Interventions	Ty21a vaccines: doses of gelatin capsules given 2 days apart, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	One active arm of multi-arm study
Allocation concealment	A
Study	Levine 1990 A
Methods	Intermediate surveillance Randomization by classroom Followup 3 yrs
Participants	Ages 5-19 yrs. Chile
Interventions	Ty21a, liquid formulation, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	
Allocation concealment	A
Study	Levine 1990 B

Methods	Intermediate surveillance Randomization by classroom Followup 3 yrs
Participants	Ages 5-19 yrs. Chile
Interventions	Ty21a, enteric capsule formulation, vs. placebo 3 doses
Outcomes	Typhoid fever documented by <i>S. typhi</i> cultured from blood, bone marrow, or duodenal fluid
Notes	
Allocation concealment	A
Study	Polish Ty Com 1966 A
Methods	Surveillance method not described Followup 3 yrs
Participants	Ages 5-14 yrs Poland
Interventions	Inactivated vaccine (acetone) vs. tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i> ; minority had only clinical and serological findings
Notes	Data for efficacy of 1 dose are derived from subjects randomized to, but failing to complete, 2-dose regimen. Trial also studied 2 "chemical"-processed subunit vaccines, which were not extracted for this review There were 2 formulations of acetone-inactivated vaccine studied
Allocation concealment	B
Study	Polish Ty Com 1966 B
Methods	Surveillance method not described Followup 3 yrs
Participants	Ages 15-60 yrs Poland
Interventions	Inactivated vaccine (acetone) vs tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i> ; minority had only clinical and serological findings
Notes	Data for efficacy of 1 dose are derived from subjects randomized to, but failing to complete, 2-dose regimen. Trial also studied 2 "chemical"-processed subunit vaccines, which were not extracted for this review There were 2 formulations of acetone-inactivated vaccine studied
Allocation concealment	B
Study	Polish Ty Com 1966 C
Methods	Surveillance method not described Followup 3 yrs
Participants	Age 5-60 yrs Poland

Interventions	Inactivated vaccine (formol) vs. tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i> ; minority had only clinical and serological findings
Notes	Data for efficacy of 1 dose are derived from subjects randomized to, but failing to complete, 2-dose regimen. Trial also studied 2 "chemical"-processed subunit vaccines, which were not extracted for this review
Allocation concealment	B
Study	Simanjuntak 1991 A
Methods	Intermediate surveillance for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 3-44 yrs Indonesia
Interventions	Ty21a, liquid formulation, vs. placebo 3 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	A
Study	Simanjuntak 1991 B
Methods	Intermediate surveillance for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 3-44 yrs. Simanjuntak
Interventions	Ty21a, enteric capsule formulation, vs. placebo 3 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	A
Study	Tapa 1975
Methods	Surveillance method not described for efficacy Active surveillance for toxicity Followup 7.5 yrs
Participants	Ages 2-60 yrs Tonga
Interventions	Inactivated vaccine (acetone), vs. tetanus toxoid vaccine 1 or 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i> ; some cases may have been documented only with clinical findings and positive stool culture.
Notes	
Allocation concealment	A
Study	Wahdan 1982
Methods	Intermediate surveillance for efficacy

	Active surveillance for toxicity Followup 3 yrs
Participants	Ages 6-7 yrs Egypt
Interventions	Ty21a vaccine, vs. placebo 3 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	A
Study	Yug Ty Comm 1962 A
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 6 yrs
Participants	Ages 5-50 yrs Yugoslavia
Interventions	Inactivated vaccine (heat) vs. <i>Shigella flexneri</i> vaccine 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	75% received a booster dose after the first year; in Data Table for cumulative efficacy at 3 years, these subjects are included
Allocation concealment	B
Study	Yug Ty Comm 1962 B
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 6 yrs
Participants	Ages 5-50 yrs Yugoslavia
Interventions	Inactivated vaccine (alcohol) vs. <i>Shigella flexneri</i> vaccine 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	75% received a booster dose after the first year; in Data Table for cumulative efficacy at 3 years, these subjects are included
Allocation concealment	B
Study	Yug Ty Comm 1964 A
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 2-60 Yugoslavia
Interventions	Inactivated vaccine (acetone) vs. tetanus toxoid 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	B

Study	Yug Ty Comm 1964 B
Methods	Passive surveillance for efficacy Active surveillance for toxicity Followup 2.5 yrs
Participants	Ages 2-60 yrs Yugoslavia
Interventions	Inactivated vaccine (heat) vs. tetanus toxoid 2 doses
Outcomes	Typhoid fever documented by blood cultures positive for <i>S. typhi</i>
Notes	
Allocation concealment	B

Characteristics of excluded studies

Study	Reason for exclusion
Chuttani 1977	These reports describe efficacy observed in three randomized controlled trials of killed oral vaccines, which were ineffective vaccines no longer in use.
Ferreccio 1989	This randomized trial had a control arm in which subjects did not receive typhoid vaccine.
Hejfec 1976	This report describes three randomized controlled trials—one examined efficacy of an aerosolized vaccine, two examined efficacy of killed oral vaccines. Neither type was effective and neither is in clinical use.
Hejfec USSR 1-2 1965	Two separate randomized trials, described together. None of chemical subunit vaccines that were studied is in use.

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GRAPHS

To view a graph or table, click on the outcome title of the summary table below.

To view graphs using MetaView: select "Outline" on the menu bar, then scroll down to Links and then click on Metaview graphs.

01 Vi vaccine vs. control: efficacy				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 One dose, Year 1</u>	2	18291	Peto OR [95% CI]	0.36 [0.23, 0.57]
<u>02 One dose, Year 2</u>	1	11384	Peto OR [95% CI]	0.49 [0.26, 0.94]
<u>03 One dose, Year 3</u>	1	11384	Peto OR [95% CI]	0.51 [0.24, 1.09]
<u>04 Cumulative to 2.5-3 yrs, 1 dose</u>	1	11384	Peto OR [95% CI]	0.47 [0.31, 0.70]
02 Ty21a vaccine vs. control: efficacy				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 Three doses, Year 1</u>	4	107275	Peto OR [95% CI]	0.58 [0.45, 0.75]
<u>02 Three doses, Year 2</u>	4	107275	Peto OR [95% CI]	0.45 [0.35, 0.58]
<u>03 Three doses, Year 3</u>	4	107275	Peto OR [95% CI]	0.46 [0.30, 0.68]
<u>04 Three doses, Year 4</u>	1	44076	Peto OR [95% CI]	0.28 [0.12, 0.64]
<u>05 Three doses, Year 5</u>	1	44076	Peto OR [95% CI]	0.54 [0.24, 1.22]
<u>06 Two doses, Year 1</u>	1	54925	Peto OR [95% CI]	0.49 [0.33, 0.74]
<u>07 Two doses, Year 2</u>	1	54925	Peto OR [95% CI]	0.33 [0.19, 0.57]
<u>08 Two doses, Year 3</u>	1	54925	Peto OR [95% CI]	0.78 [0.40, 1.53]
<u>09 Two doses, Year 4</u>	1	54925	Peto OR [95% CI]	0.81 [0.47, 1.41]
<u>10 Two doses, Year 5</u>	1	54925	Peto OR [95% CI]	0.93 [0.47, 1.84]
<u>11 One dose, Year 1</u>	1	54923	Peto OR [95% CI]	0.75 [0.52, 1.09]
<u>12 One dose, Year 2</u>	1	54923	Peto OR [95% CI]	0.65 [0.40, 1.07]
<u>13 One dose, Year 3</u>	1	54923	Peto OR [95% CI]	0.99 [0.52, 1.87]
<u>14 One dose, Year 4</u>	1	54923	Peto OR [95% CI]	1.06 [0.63, 1.77]

<u>15 One dose, Year 5</u>	1	54923	Peto OR [95% CI]	1.10 [0.57, 2.12]
<u>16 Cumulative to 2.5-3 yrs, 3 doses</u>	9	330434	Peto OR [95% CI]	0.54 [0.47, 0.61]
03 Whole cell vaccines vs. control: efficacy				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 Two doses, Year 1</u>	14	1338871	Peto OR [95% CI]	0.32 [0.27, 0.38]
<u>02 Two doses, Year 2</u>	8	823085	Peto OR [95% CI]	0.31 [0.23, 0.44]
<u>03 Two doses, Year 3</u>	8	823085	Peto OR [95% CI]	0.27 [0.17, 0.41]
<u>04 Two doses, Year 4</u>	5	130200	Peto OR [95% CI]	0.29 [0.17, 0.49]
<u>05 Two doses, Year 5</u>	5	130200	Peto OR [95% CI]	0.37 [0.24, 0.56]
<u>06 One dose, Year 1</u>	10	575547	Peto OR [95% CI]	0.36 [0.26, 0.49]
<u>07 One dose, Year 2</u>	8	261285	Peto OR [95% CI]	0.51 [0.29, 0.89]
<u>08 One dose, Year 3</u>	6	189204	Peto OR [95% CI]	0.45 [0.23, 0.85]
<u>09 One dose, Year 4</u>	3	36240	Peto OR [95% CI]	0.65 [0.19, 2.26]
<u>10 One dose, Year 5</u>	3	36240	Peto OR [95% CI]	0.24 [0.11, 0.50]
<u>11 Cumulative to 2.5-3 years, 2 doses</u>	15	1314470	Peto OR [95% CI]	0.33 [0.29, 0.37]
04 Vi vaccine vs. control: toxicity				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 Fever</u>	1	382	Peto OR [95% CI]	0.23 [0.02, 2.51]
<u>02 Swelling</u>	1	382	Peto OR [95% CI]	0.21 [0.10, 0.46]
05 Ty21a vaccine vs. control: toxicity				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 Fever</u>	3	3662	Peto OR [95% CI]	1.80 [1.00, 3.22]
<u>02 Vomiting</u>	3	3662	Peto OR [95% CI]	2.11 [1.01, 4.40]

<u>03 Diarrhea</u>	2	1190	Peto OR [95% CI]	0.90 [0.51, 1.62]
06 Whole cell vaccines vs. control: toxicity				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 Fever</u>	14	30794	Peto OR [95% CI]	1.96 [1.85, 2.08]
<u>02 Swelling</u>	12	30051	Peto OR [95% CI]	1.54 [1.45, 1.64]
<u>03 Missed school or work</u>	7	1746	Peto OR [95% CI]	2.29 [1.66, 3.17]

COVER SHEET

Title	Vaccines for preventing typhoid fever
Reviewer(s)	Engels EA, Lau J
Contribution of reviewer(s)	Information not supplied by reviewer
Issue protocol first published	Information not available
Issue review first published	1998/4
Date of most recent amendment	Information not available
Date of most recent SUBSTANTIVE amendment	19 August 1998
Most recent changes	Information not supplied by reviewer
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Dr Eric Engels Senior Staff Fellow Viral Epidemiology Branch National Cancer Institute 6130 Executive Blvd, EPN 434 Rockville

	MD USA (617-496-8115 engelse@exchange.nih.gov
Cochrane Library number	CD001261
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Internal sources of support

- No sources of support supplied

SYNOPSIS

Synopsis pending

Index Terms

Medical Subject Headings (MeSH)

Adolescent ; Adult ; Child ; Child, Preschool ; Salmonella typhi [immunology]; Typhoid Fever [immunology] [prevention & control]; Typhoid-Paratyphoid Vaccines [administration & dosage] [therapeutic use]; Vaccines, Attenuated [administration & dosage] [therapeutic use]

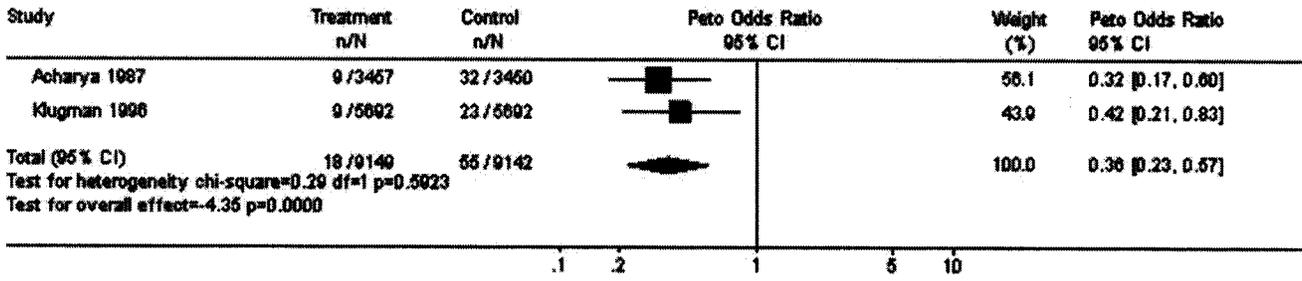
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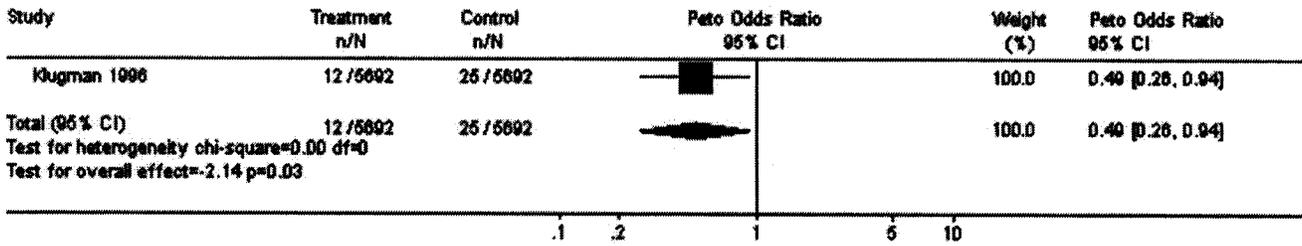
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GRAPHS

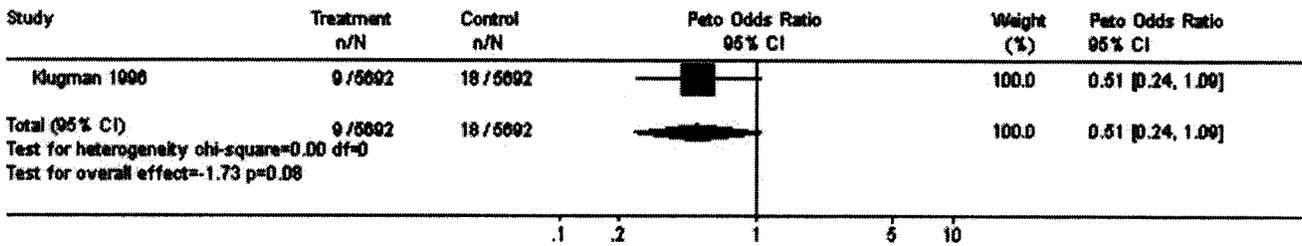
Review: Vaccines for preventing typhoid fever
 Comparison: 01 V vaccine vs. control: efficacy
 Outcome: 01 One dose, Year 1



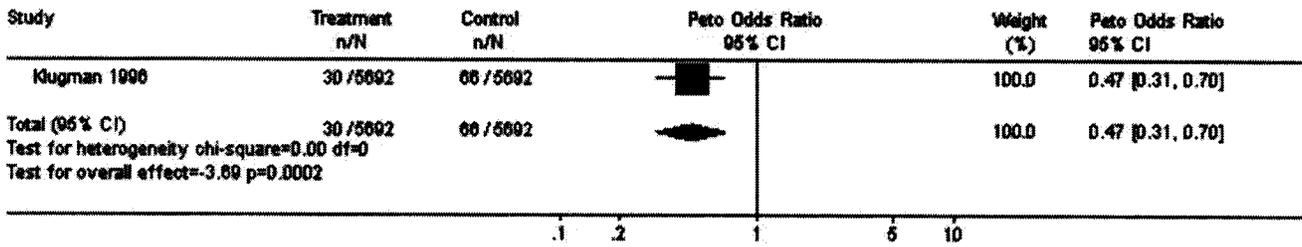
Review: Vaccines for preventing typhoid fever
 Comparison: 01 V vaccine vs. control: efficacy
 Outcome: 02 One dose, Year 2



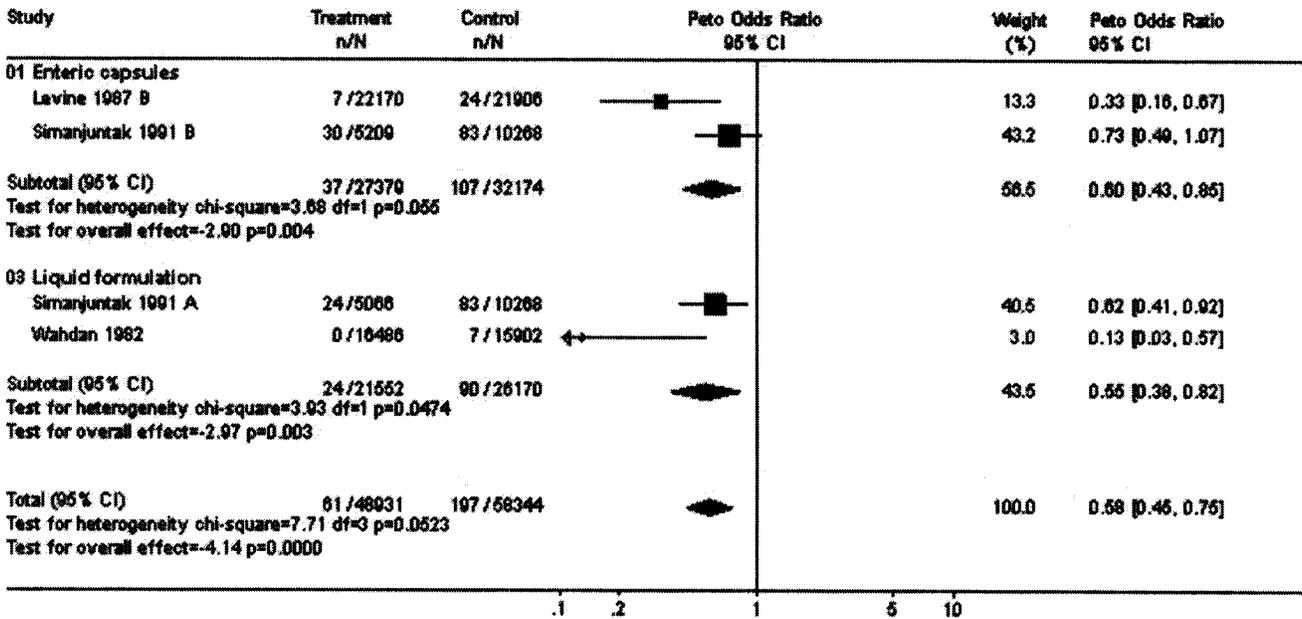
Review: Vaccines for preventing typhoid fever
 Comparison: 01 V vaccine vs. control: efficacy
 Outcome: 03 One dose, Year 3



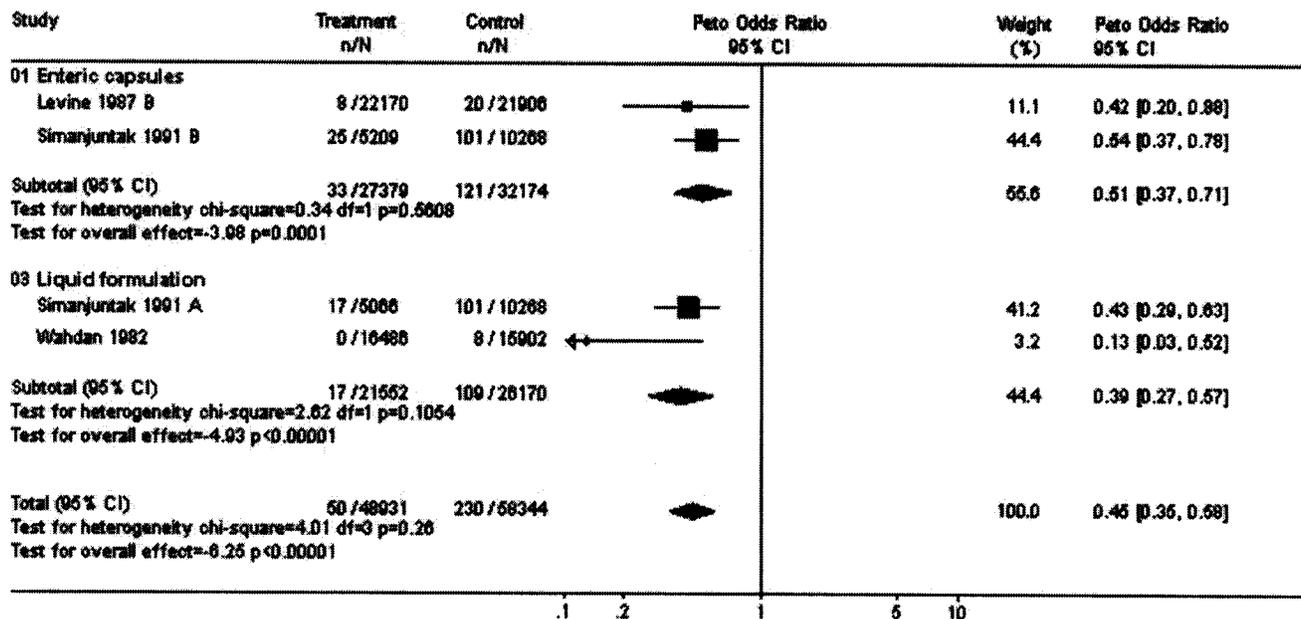
Review: Vaccines for preventing typhoid fever
 Comparison: 01 Vi vaccine vs. control: efficacy
 Outcome: 04 Cumulative to 2.5-3 yrs, 1 dose



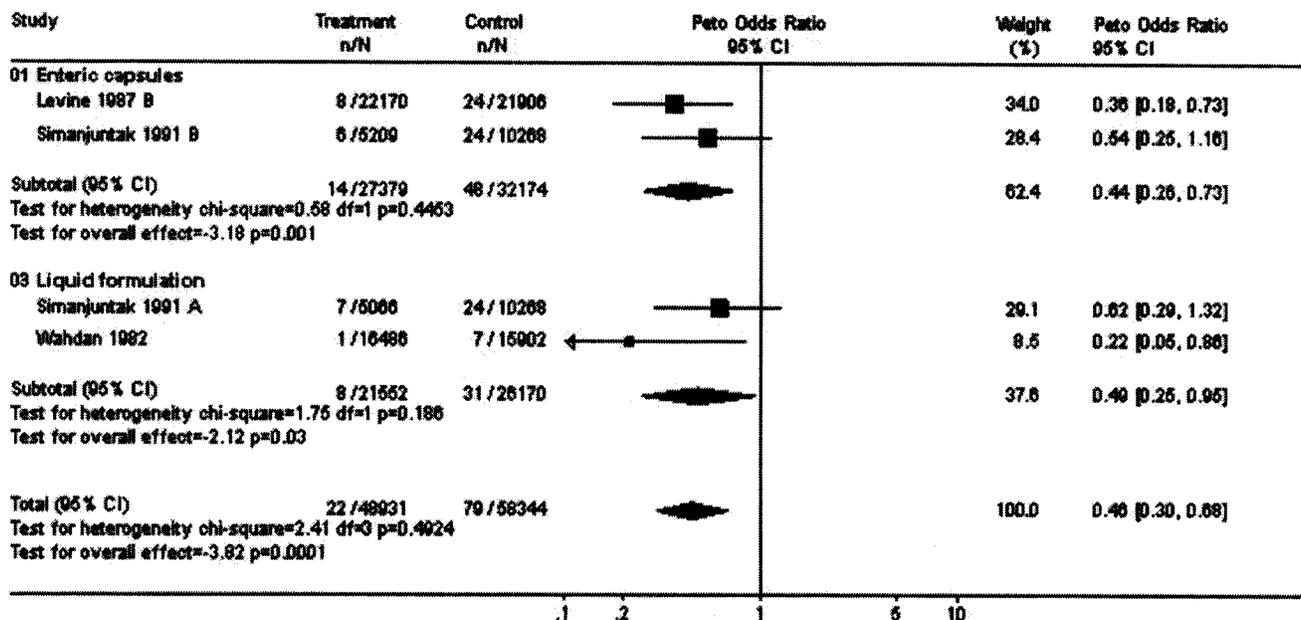
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 01 Three doses, Year 1



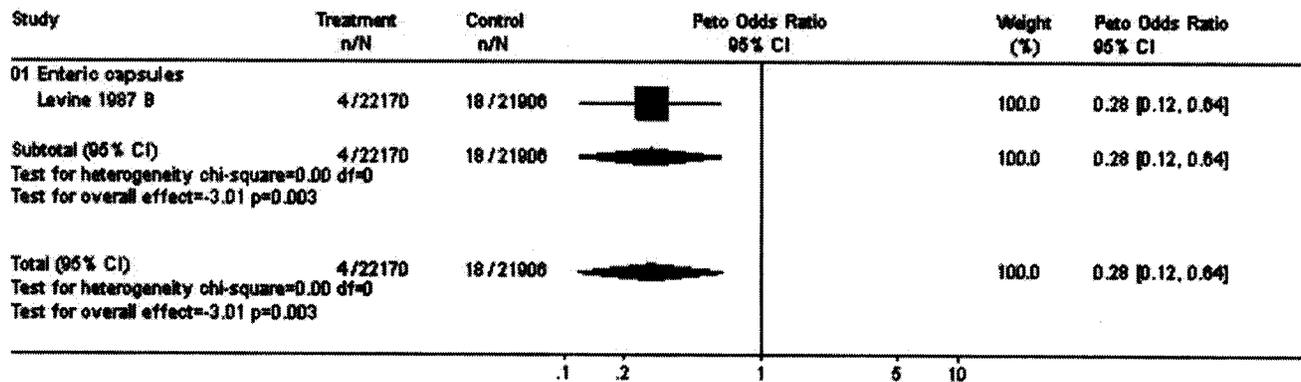
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 02 Three doses, Year 2



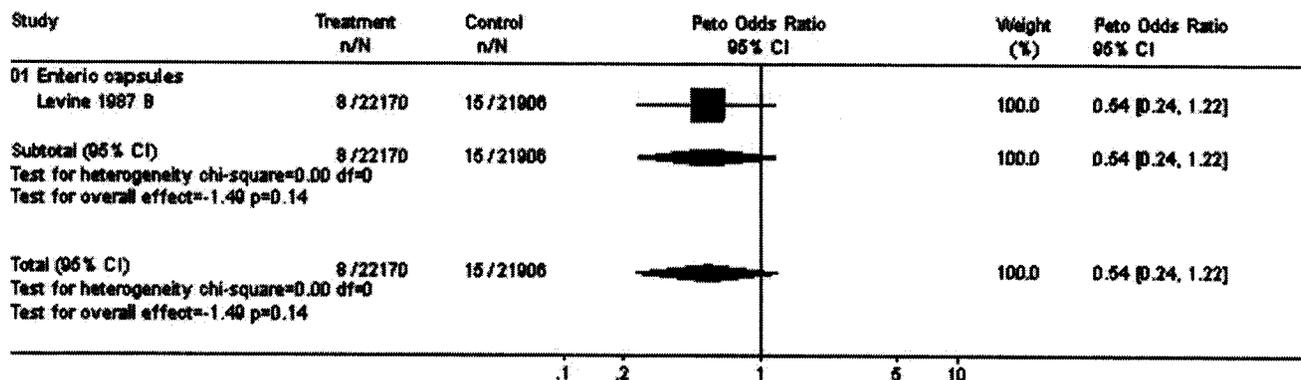
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 03 Three doses, Year 3



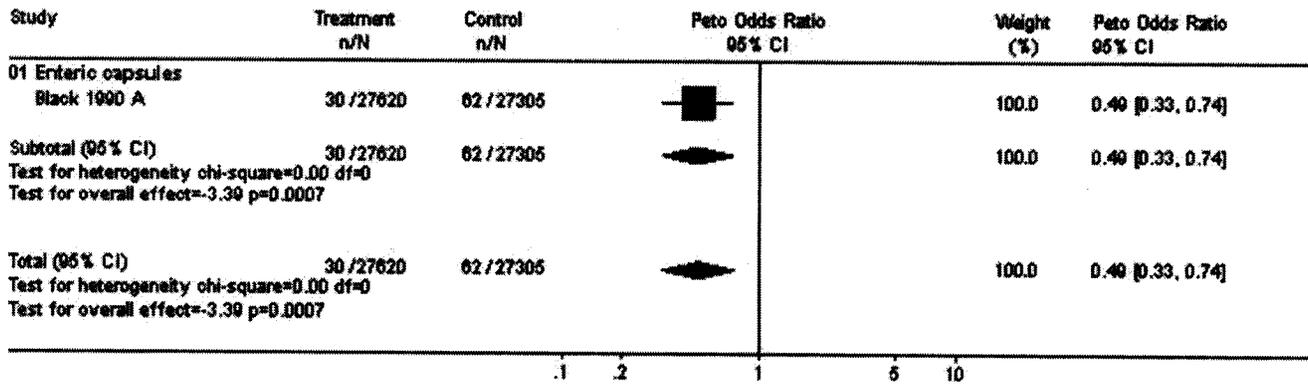
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 04 Three doses, Year 4



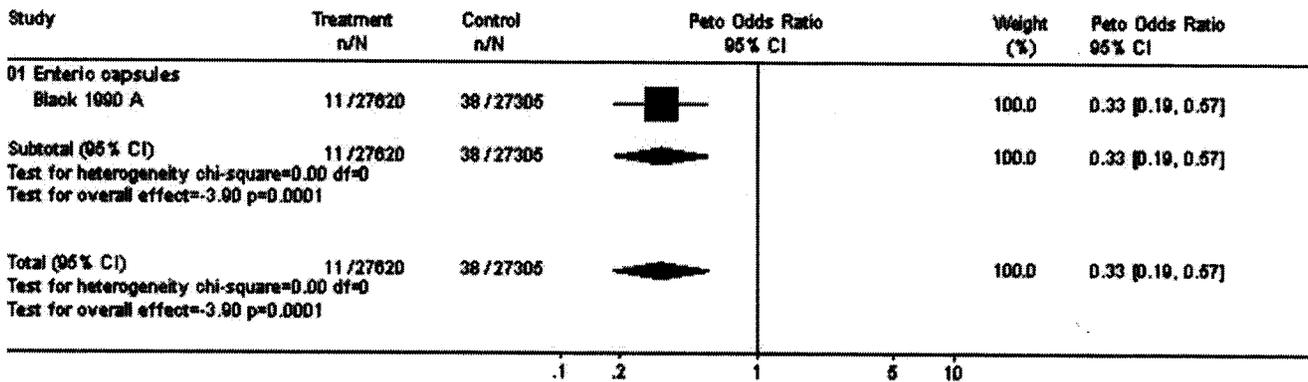
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 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 05 Three doses, Year 5



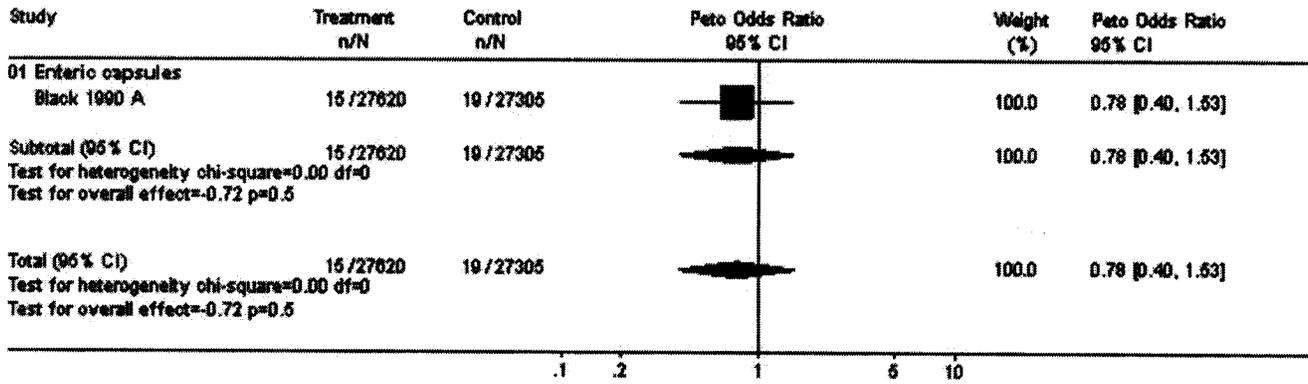
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 06 Two doses, Year 1



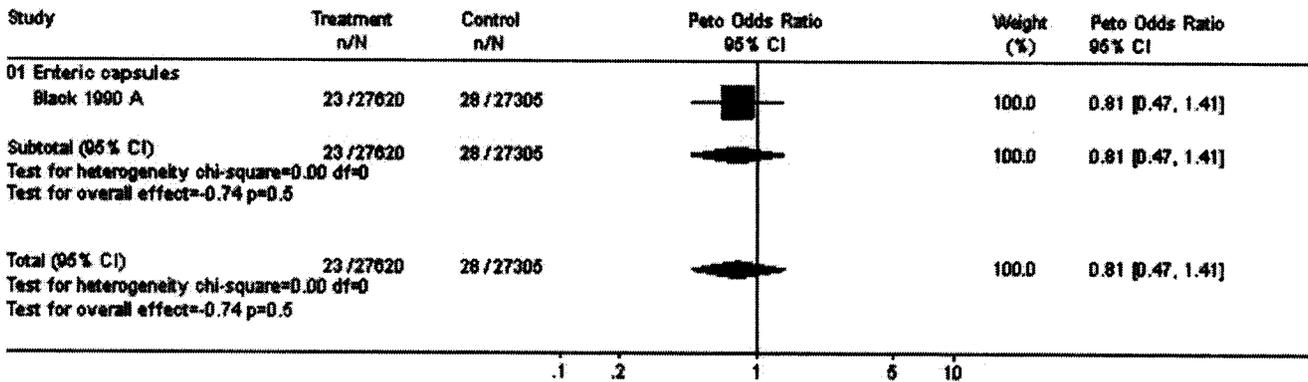
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 07 Two doses, Year 2



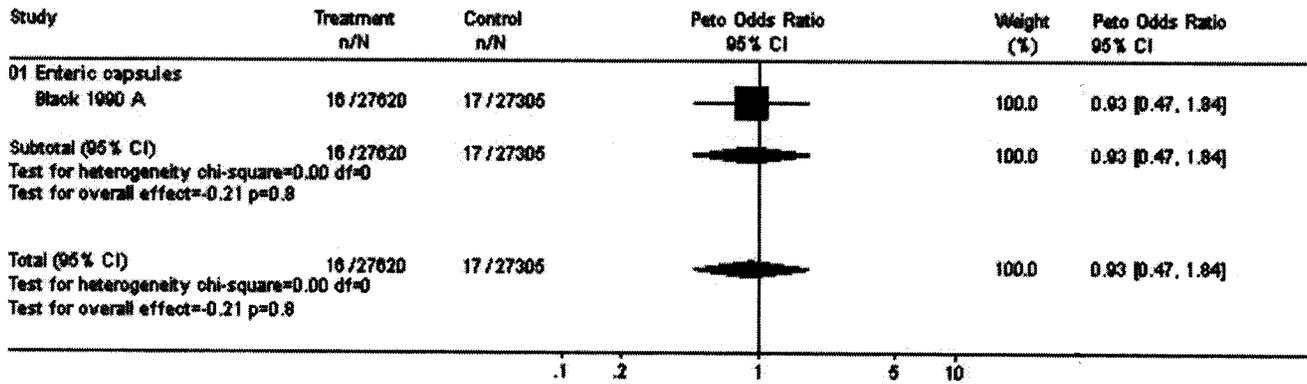
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 08 Two doses, Year 3



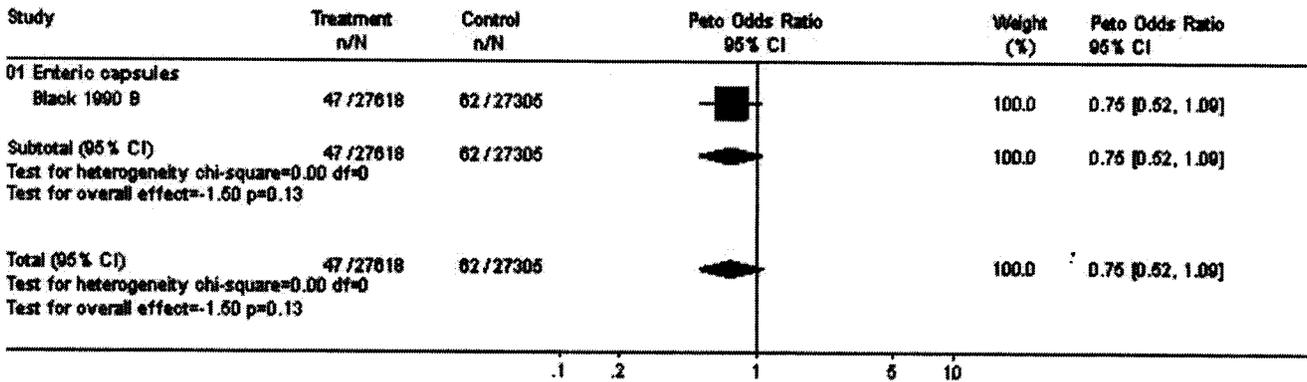
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 09 Two doses, Year 4



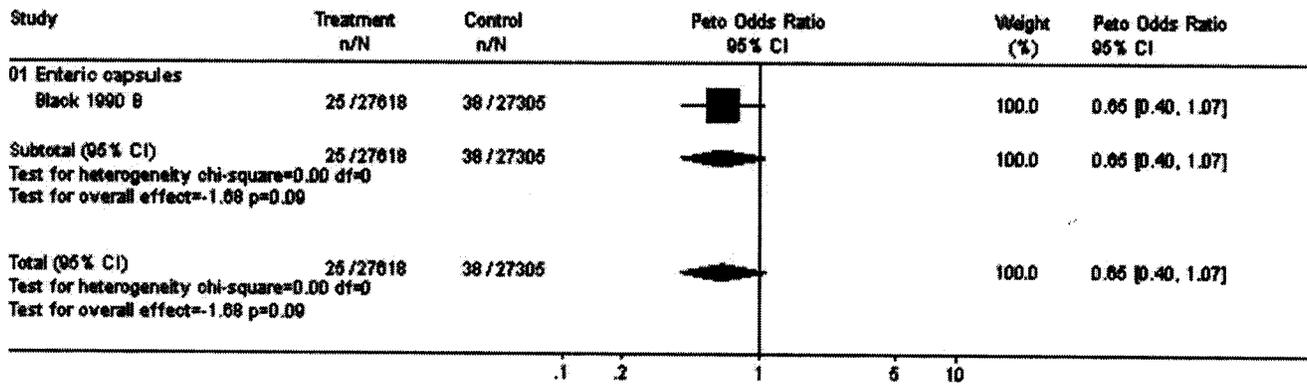
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 10 Two doses, Year 5



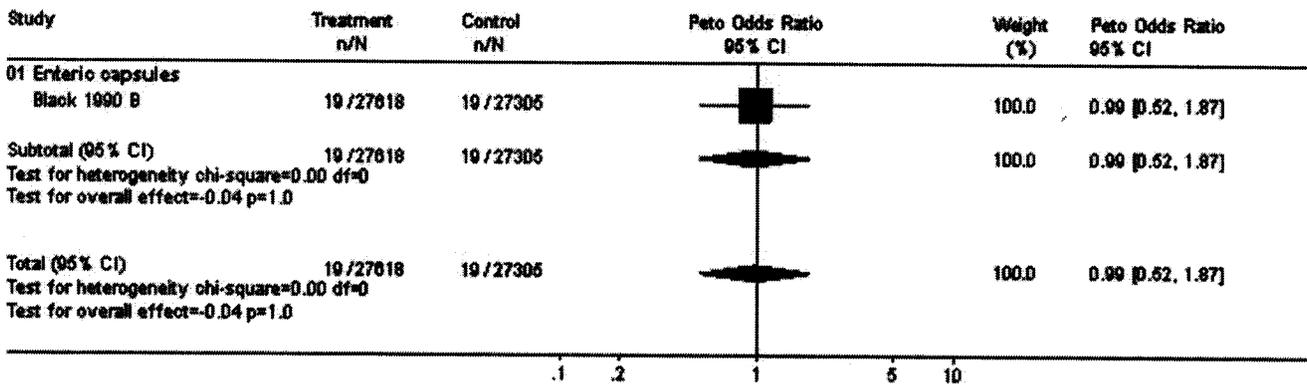
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 11 One dose, Year 1



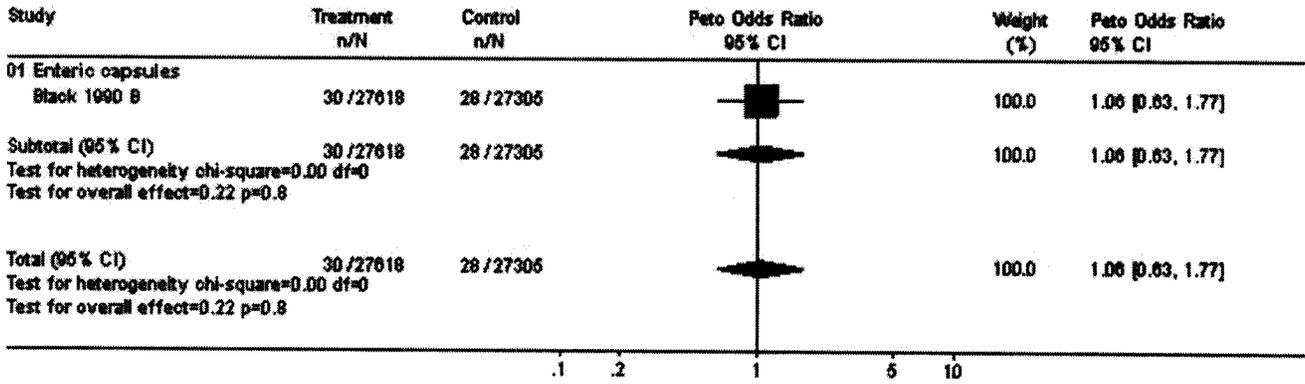
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 12 One dose, Year 2



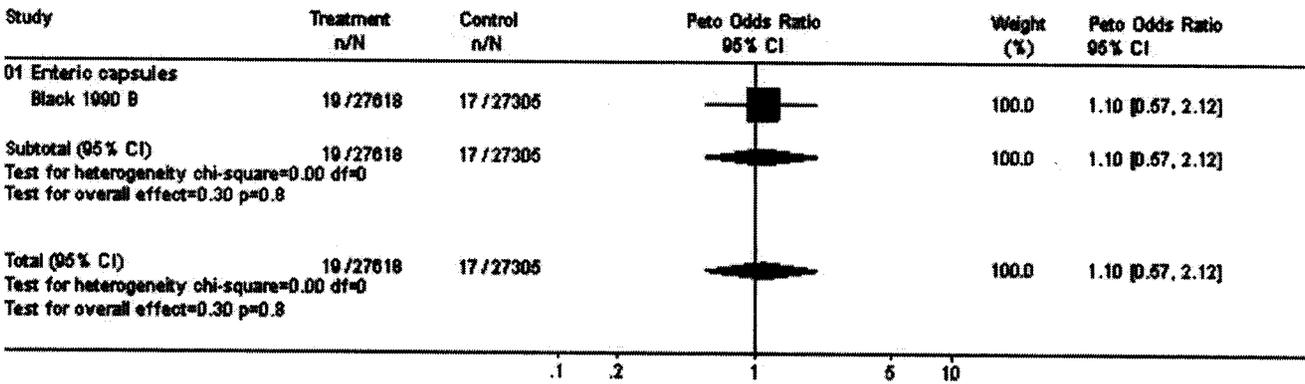
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 13 One dose, Year 3



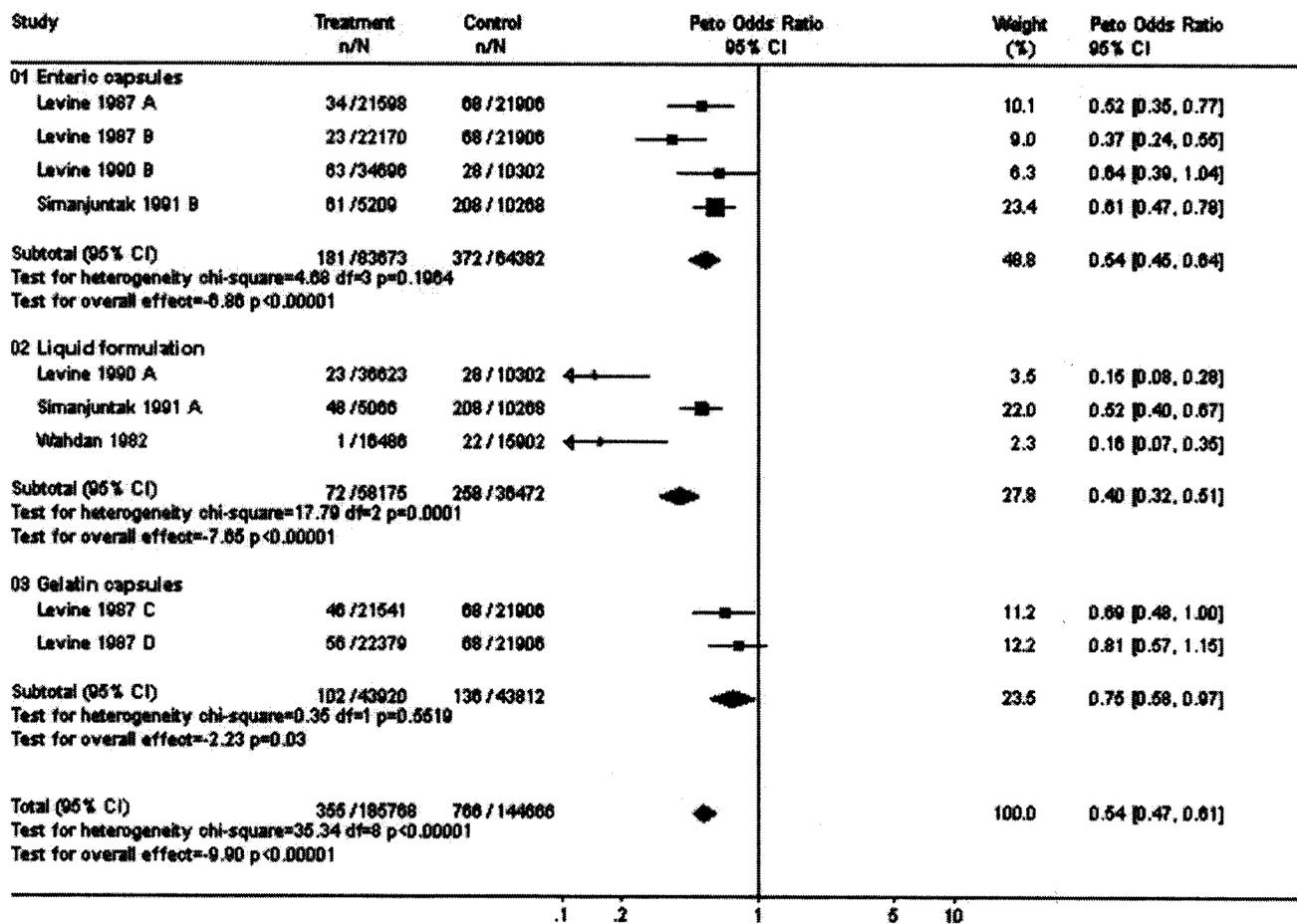
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 14 One dose, Year 4



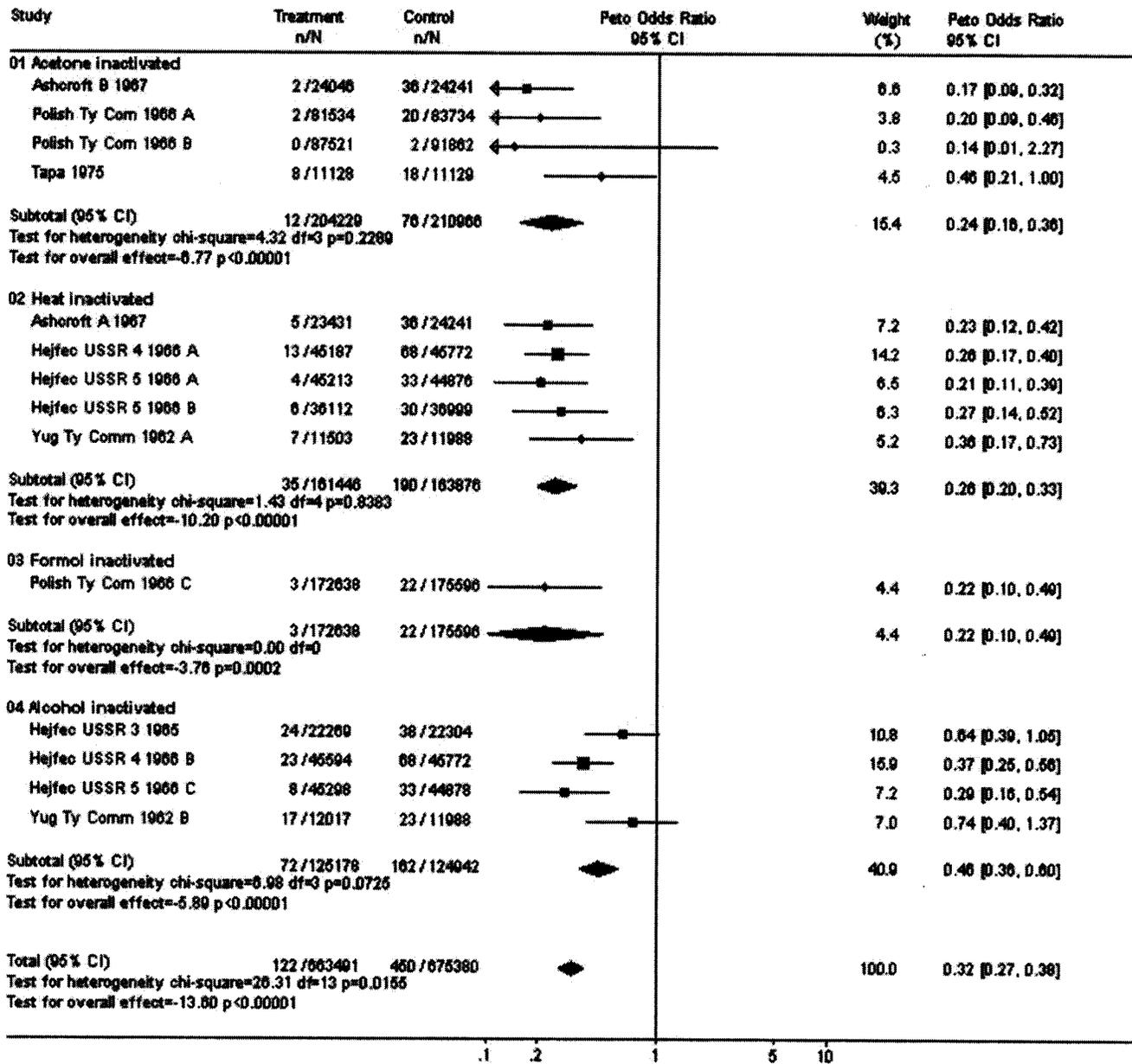
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 15 One dose, Year 5



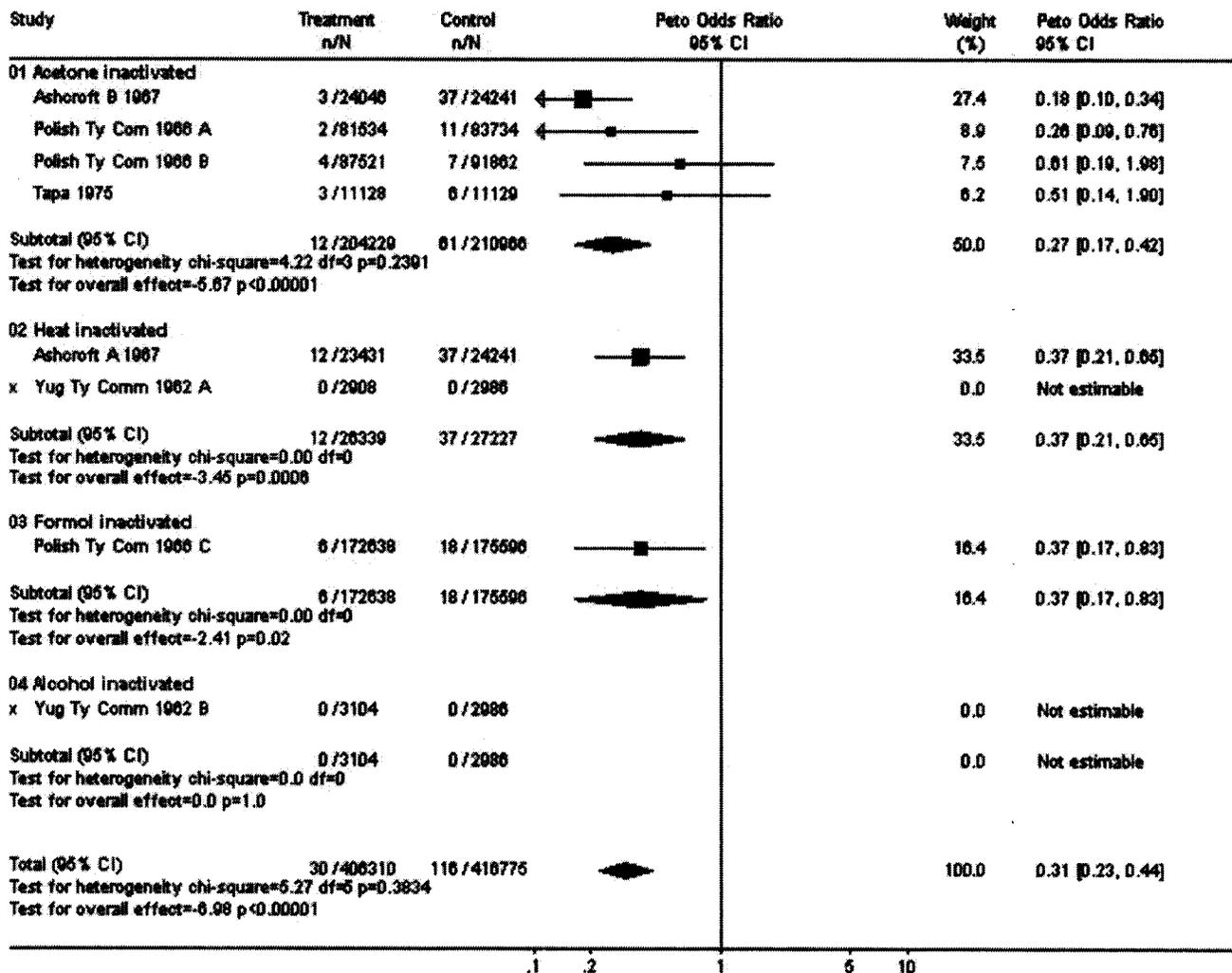
Review: Vaccines for preventing typhoid fever
 Comparison: 02 Ty21a vaccine vs. control: efficacy
 Outcome: 16 Cumulative to 2.5-3 yrs, 3 doses



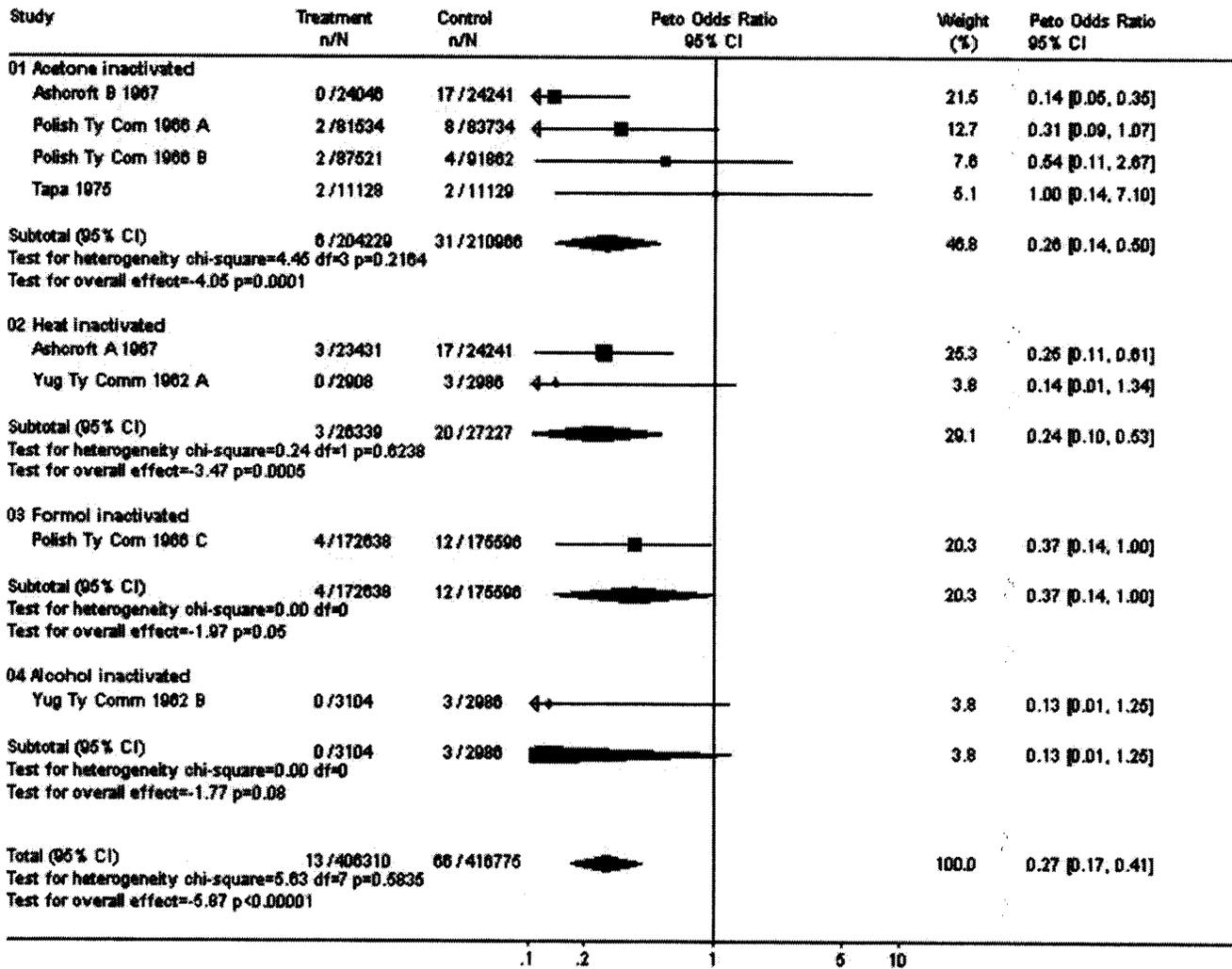
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 01 Two doses, Year 1



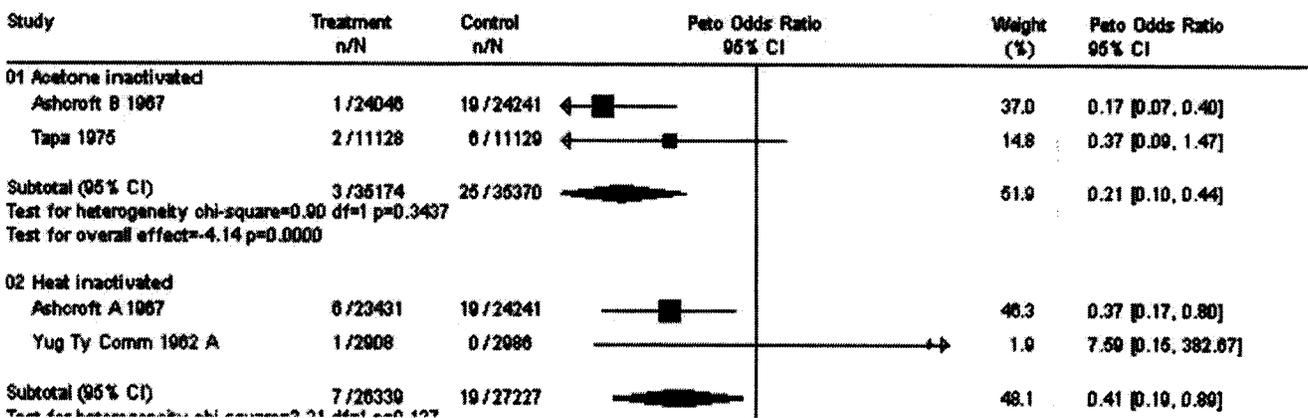
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 02 Two doses, Year 2



Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 03 Two doses, Year 3



Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 04 Two doses, Year 4



Test for heterogeneity chi-square=2.21 df=1 p=0.137
 Test for overall effect=-2.27 p=0.02

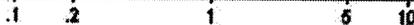
03 Formol inactivated

Subtotal (95% CI) 0 / 0 0 / 0 0.0 Not estimable
 Test for heterogeneity chi-square=0.0 df=0
 Test for overall effect=0.0 p=1.0

04 Alcohol inactivated

x Yug Ty Comm 1962 B 0 / 3104 0 / 2986 0.0 Not estimable
 Subtotal (95% CI) 0 / 3104 0 / 2986 0.0 Not estimable
 Test for heterogeneity chi-square=0.0 df=0
 Test for overall effect=0.0 p=1.0

Total (95% CI) 10 / 64617 44 / 65583 100.0 0.29 [0.17, 0.49]
 Test for heterogeneity chi-square=4.65 df=3 p=0.1994
 Test for overall effect=-4.56 p=0.0000

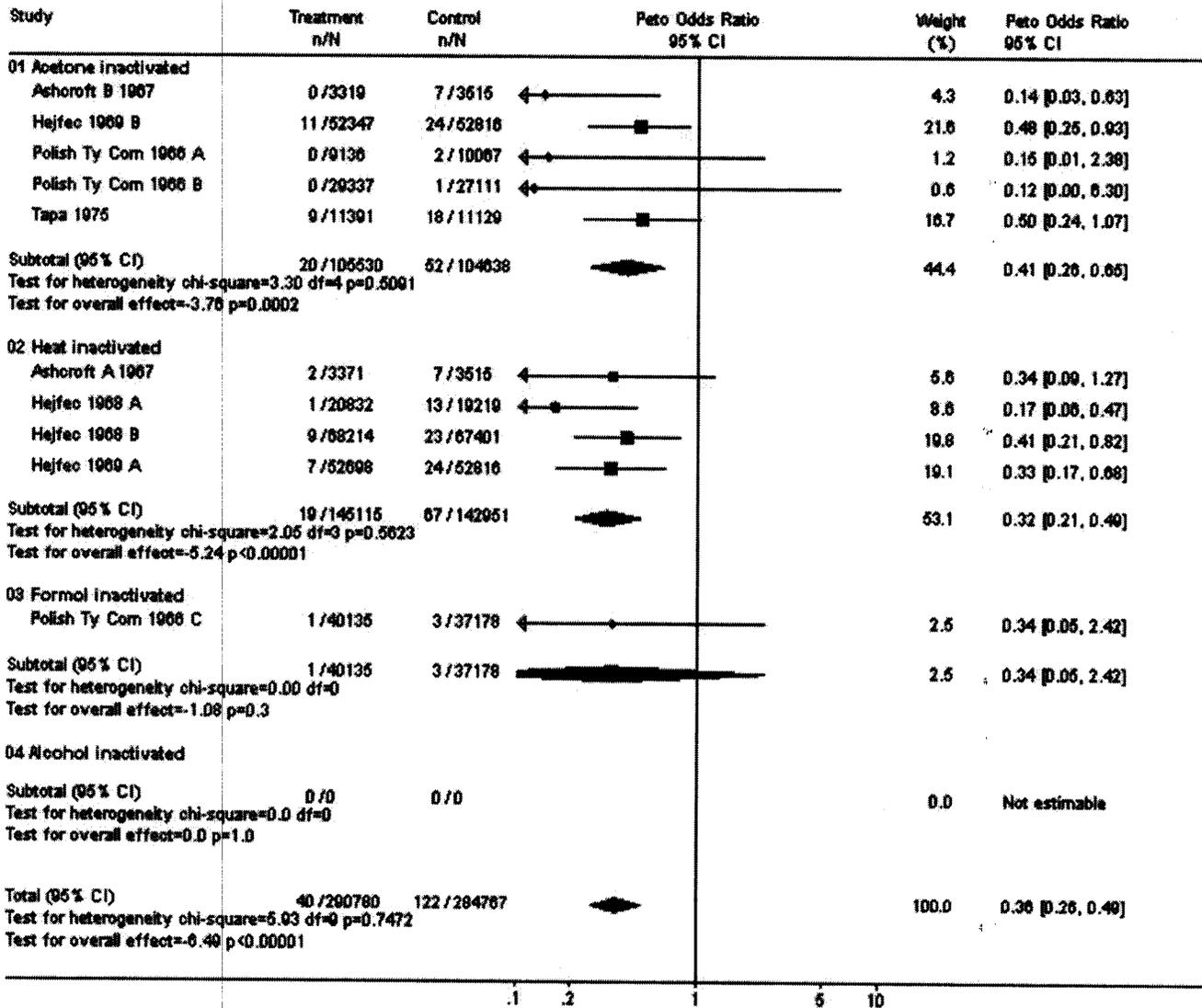


Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 05 Two doses, Year 5

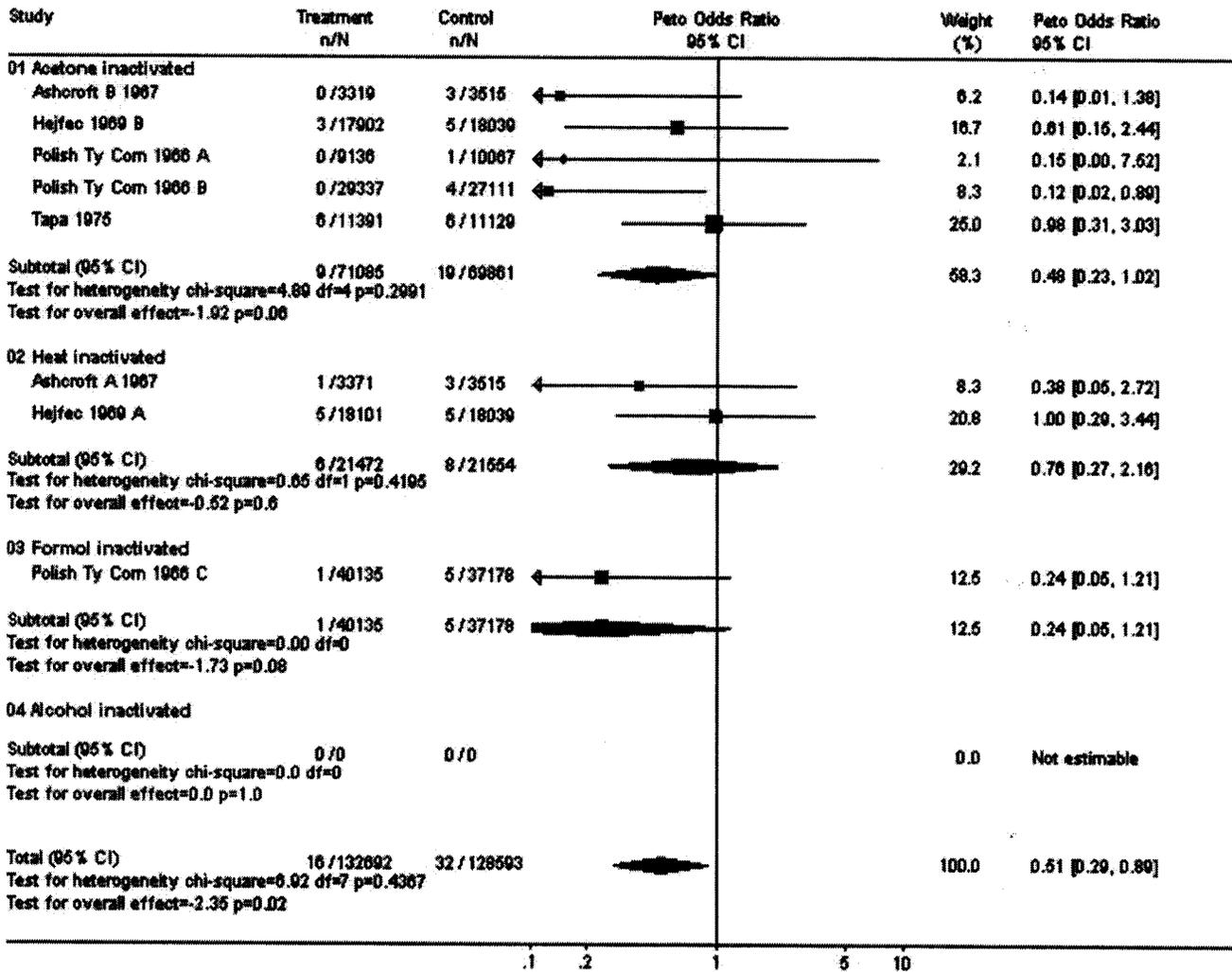
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Acetone inactivated					
Ashcroft B 1967	5 / 24046	24 / 24241		34.1	0.27 [0.13, 0.56]
Tapa 1975	5 / 11128	14 / 11129		22.4	0.39 [0.16, 0.95]
Subtotal (95% CI)	10 / 35174	38 / 35370		56.5	0.31 [0.18, 0.55]
Test for heterogeneity chi-square=0.36 df=1 p=0.5477 Test for overall effect=-4.03 p=0.0001					
02 Heat inactivated					
Ashcroft A 1967	10 / 23431	24 / 24241		40.0	0.46 [0.23, 0.89]
Yug Ty Comm 1962 A	0 / 2908	1 / 2986		1.2	0.14 [0.00, 7.00]
Subtotal (95% CI)	10 / 26339	25 / 27227		41.2	0.44 [0.23, 0.85]
Test for heterogeneity chi-square=0.34 df=1 p=0.5598 Test for overall effect=-2.44 p=0.01					
03 Formol inactivated					
Subtotal (95% CI)	0 / 0	0 / 0		0.0	Not estimable
Test for heterogeneity chi-square=0.0 df=0 Test for overall effect=0.0 p=1.0					
04 Alcohol inactivated					
Yug Ty Comm 1962 B	1 / 3104	1 / 2986		2.4	0.96 [0.06, 15.39]
Subtotal (95% CI)	1 / 3104	1 / 2986		2.4	0.96 [0.06, 15.39]
Test for heterogeneity chi-square=0.00 df=0 Test for overall effect=-0.03 p=1.0					
Total (95% CI)	21 / 64617	64 / 65583		100.0	0.37 [0.24, 0.56]
Test for heterogeneity chi-square=1.75 df=4 p=0.7816 Test for overall effect=-4.59 p<0.00001					



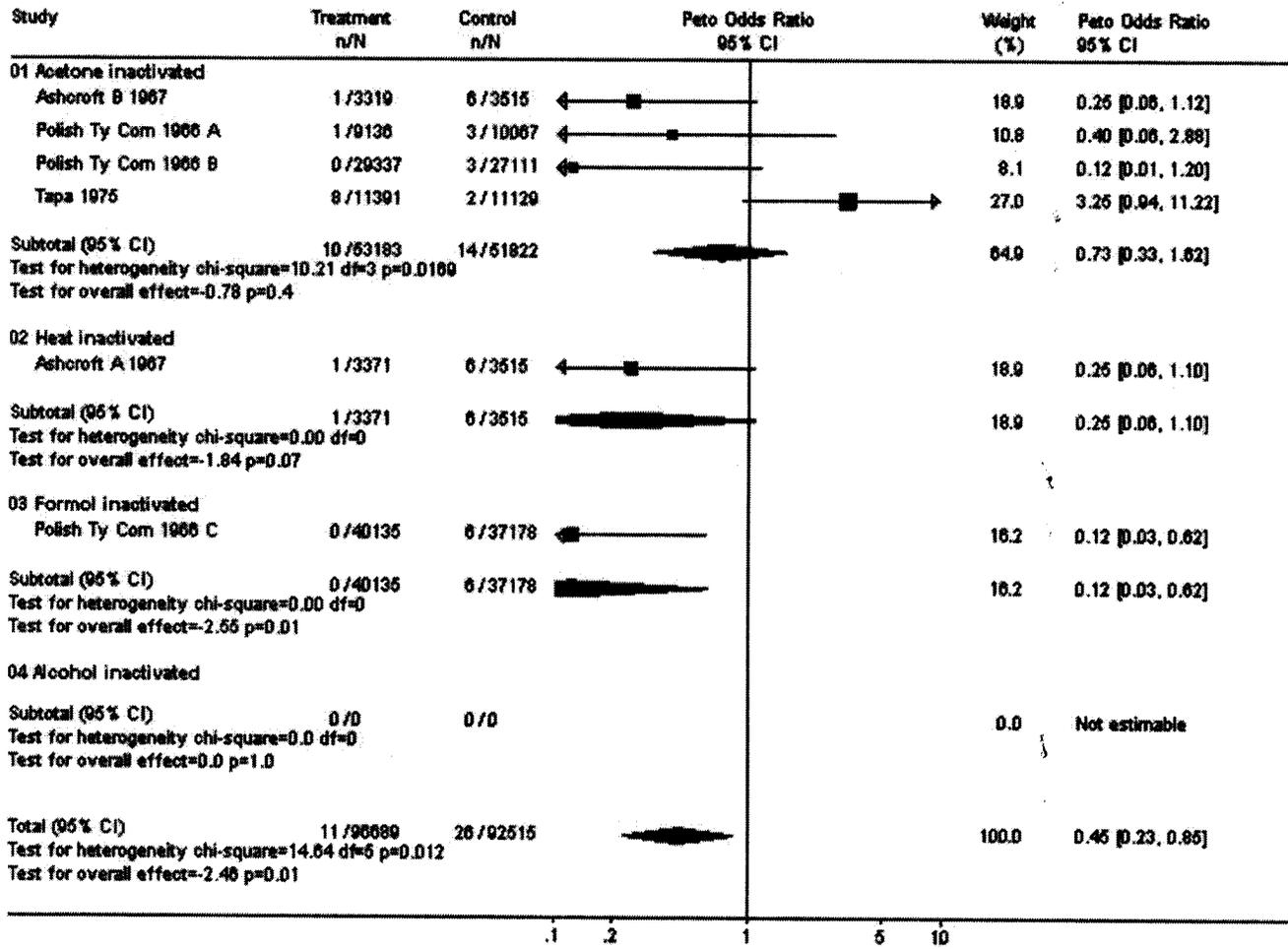
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 06 One dose, Year 1



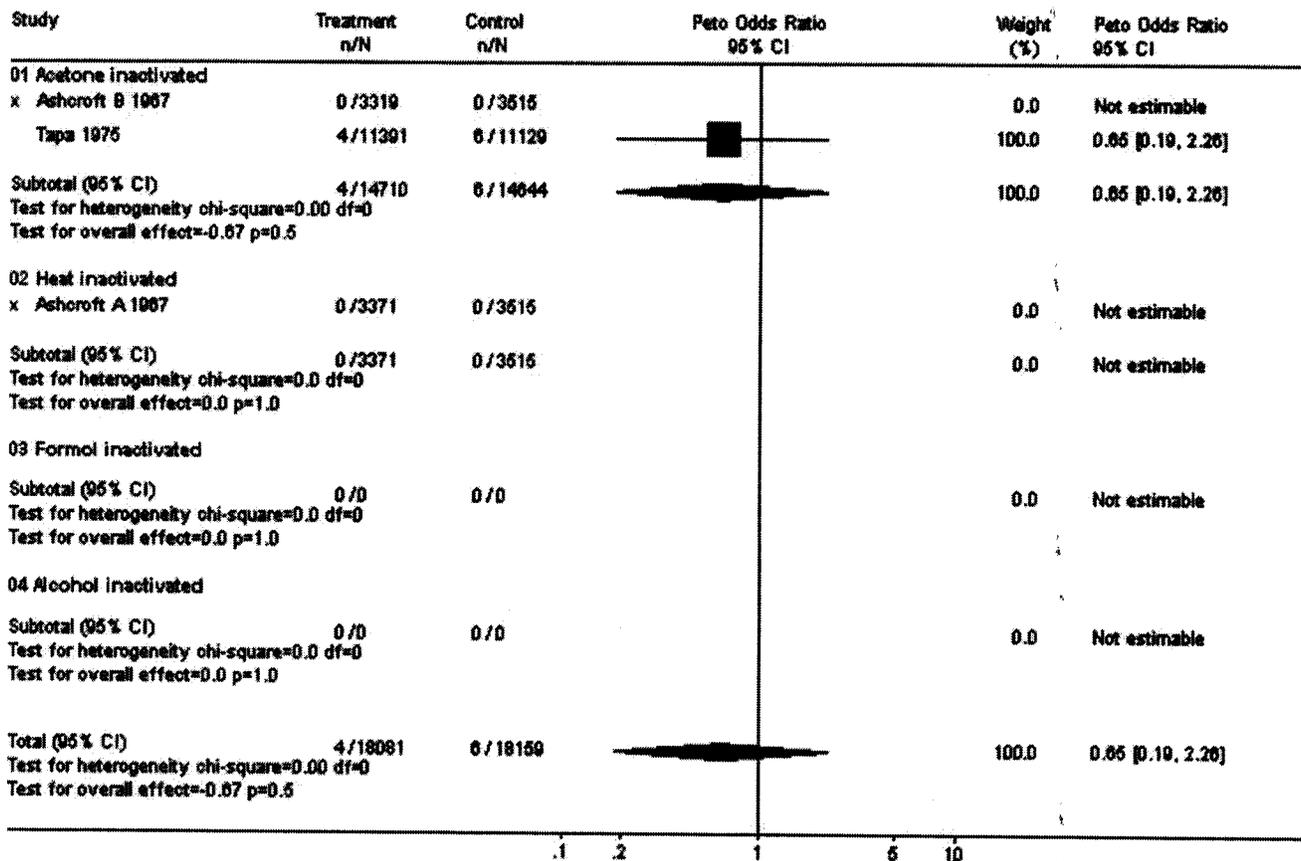
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 07 One dose, Year 2



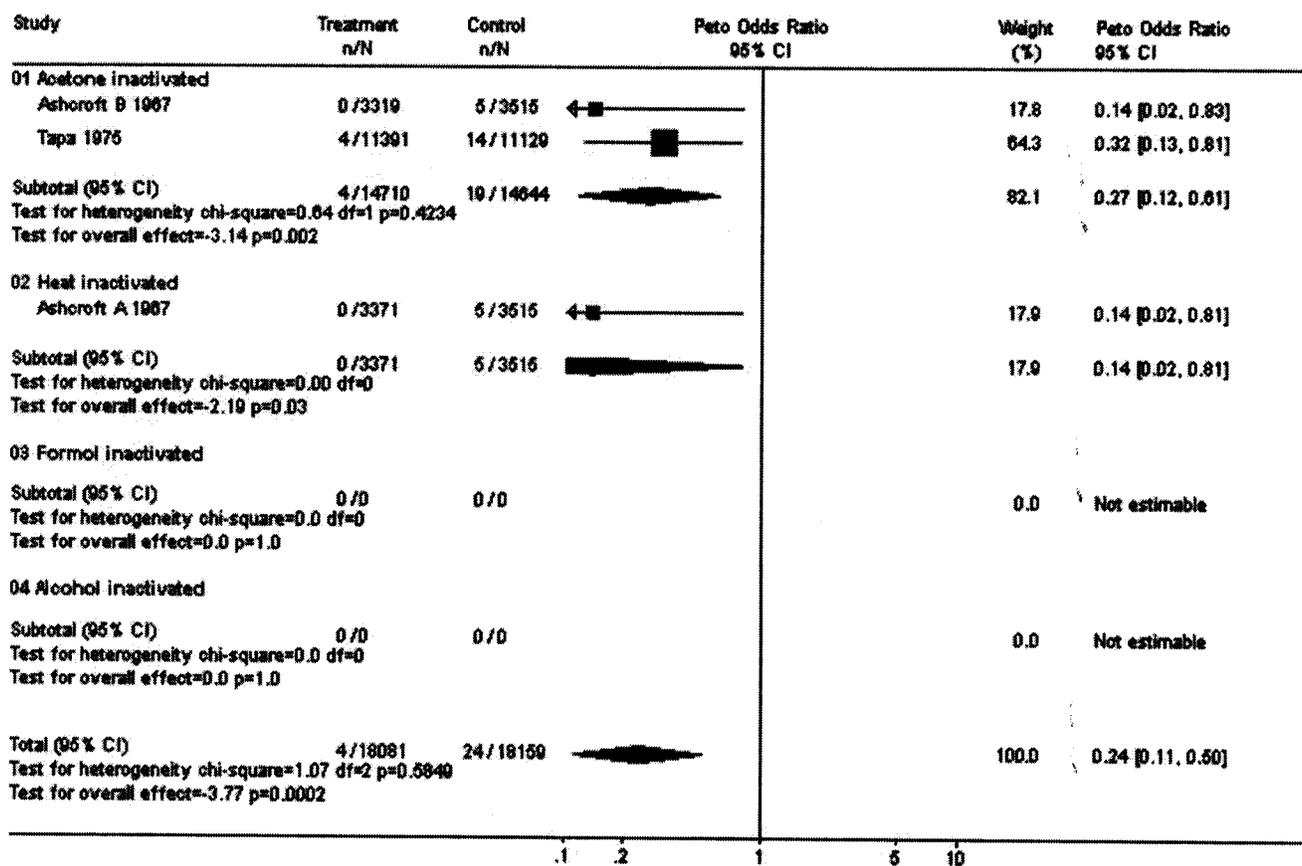
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 08 One dose, Year 3



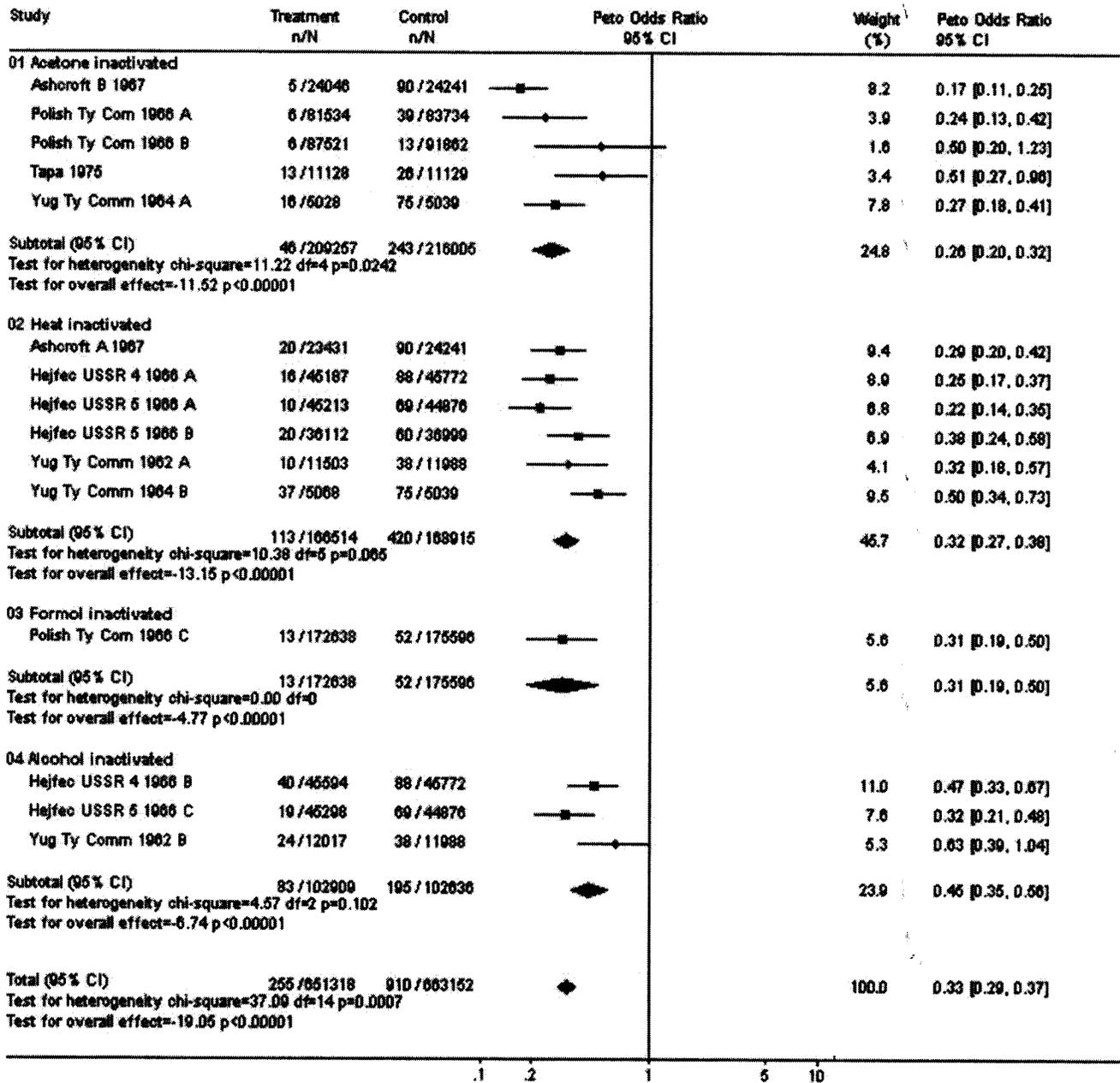
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 09 One dose, Year 4



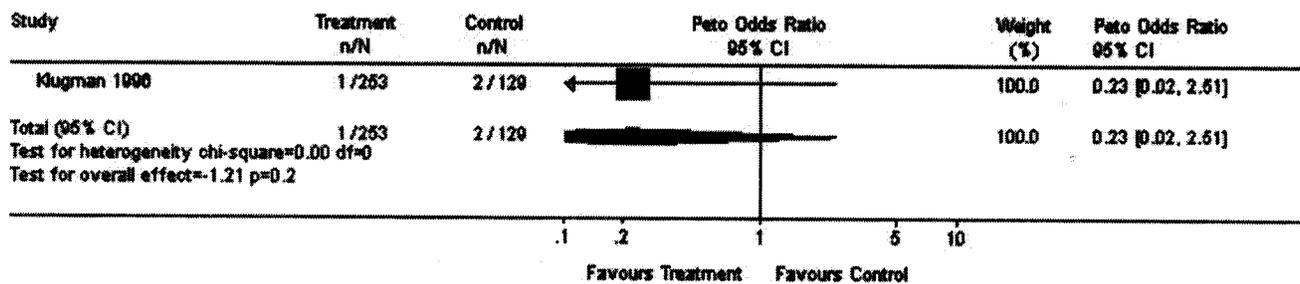
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 10 One dose, Year 5



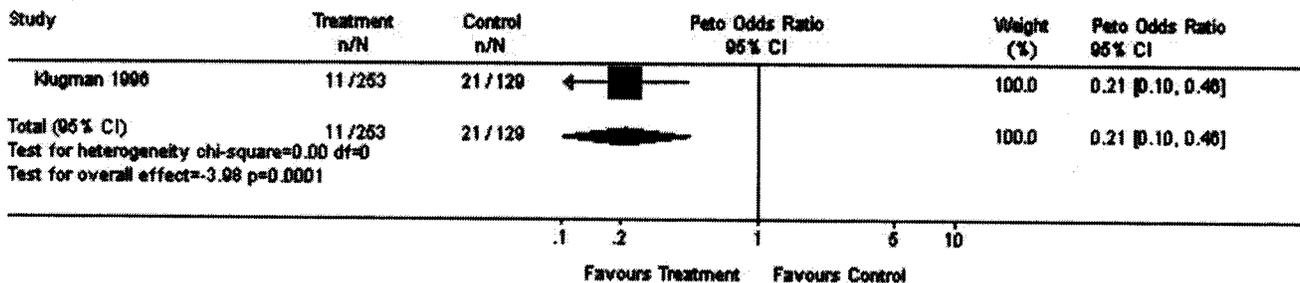
Review: Vaccines for preventing typhoid fever
 Comparison: 03 Whole cell vaccines vs. control: efficacy
 Outcome: 11 Cumulative to 2.6-3 years, 2 doses



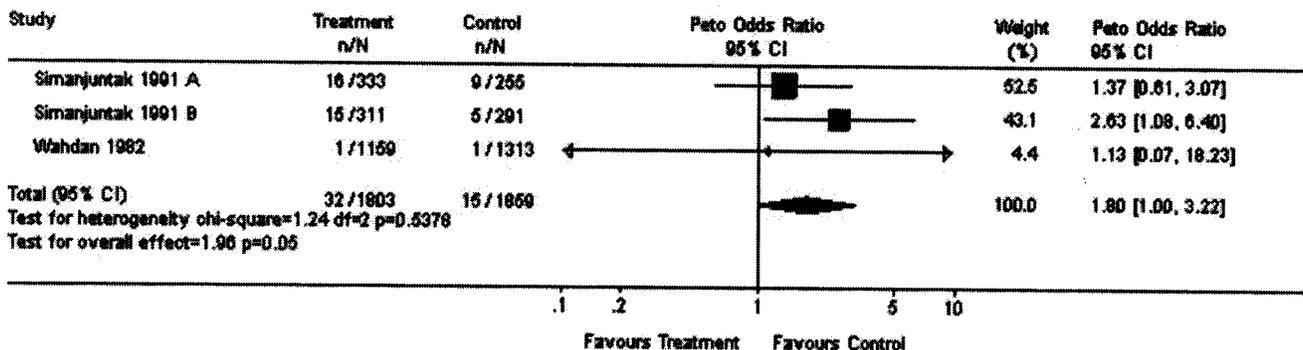
Review: Vaccines for preventing typhoid fever
 Comparison: 04 M vaccine vs. control: toxicity
 Outcome: 01 Fever



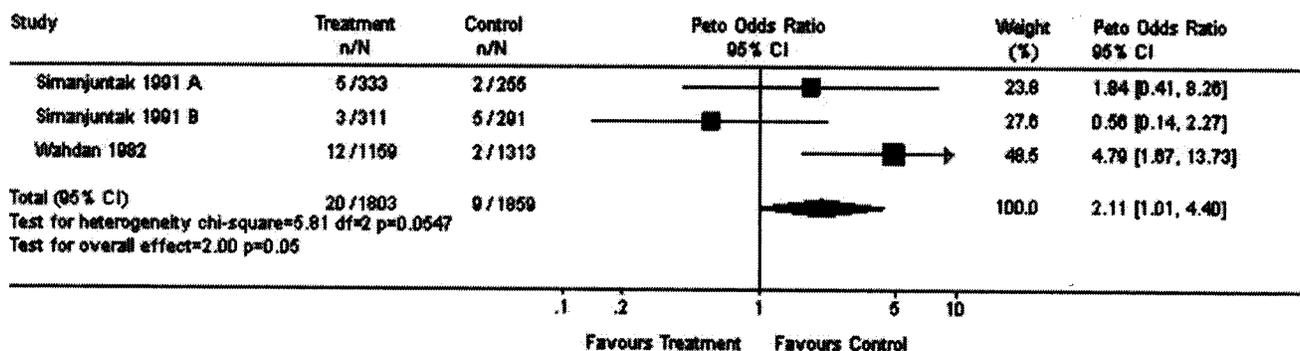
Review: Vaccines for preventing typhoid fever
 Comparison: 04 M vaccine vs. control: toxicity
 Outcome: 02 Swelling



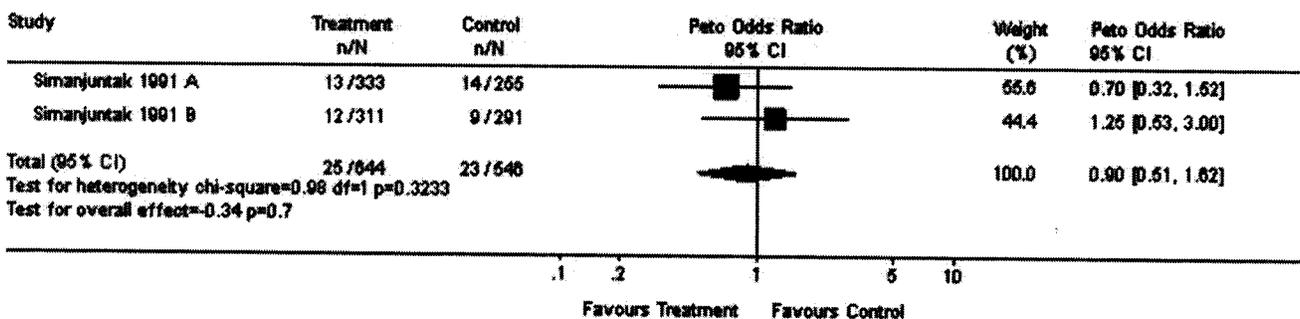
Review: Vaccines for preventing typhoid fever
 Comparison: 05 Ty21a vaccine vs. control: toxicity
 Outcome: 01 Fever



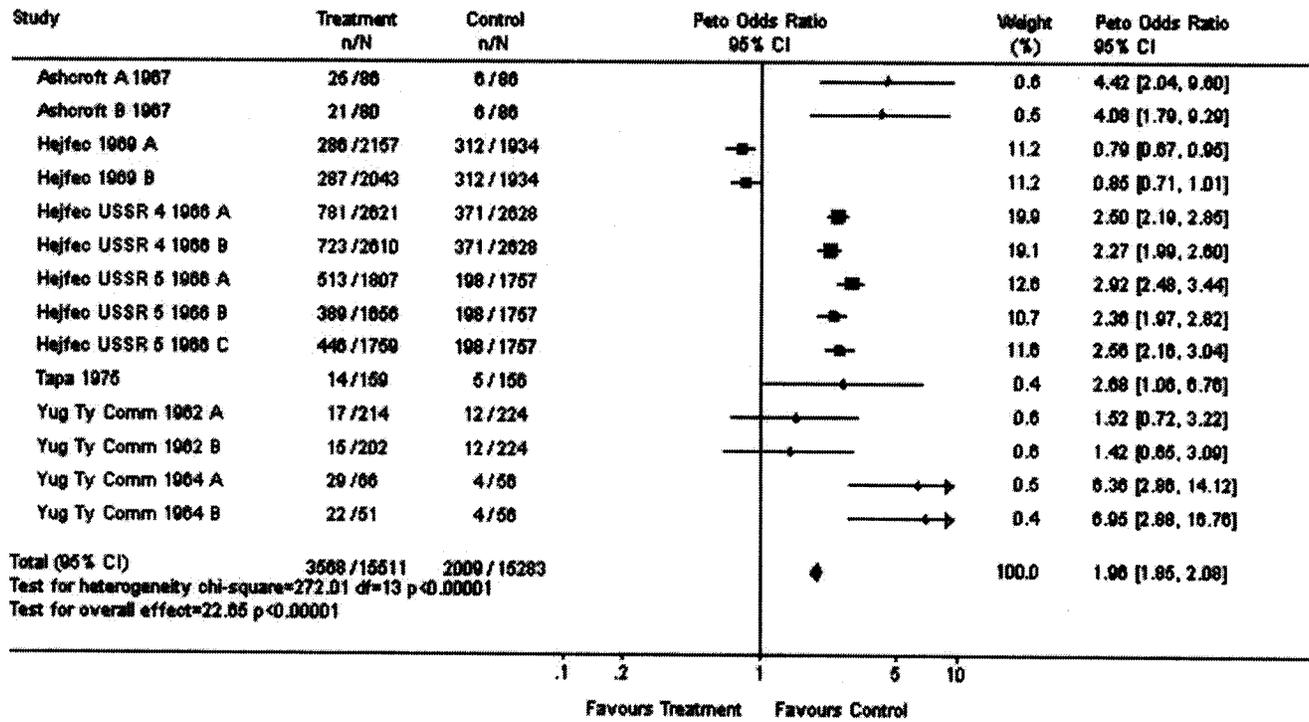
Review: Vaccines for preventing typhoid fever
 Comparison: 05 Ty21a vaccine vs. control: toxicity
 Outcome: 02 Vomiting



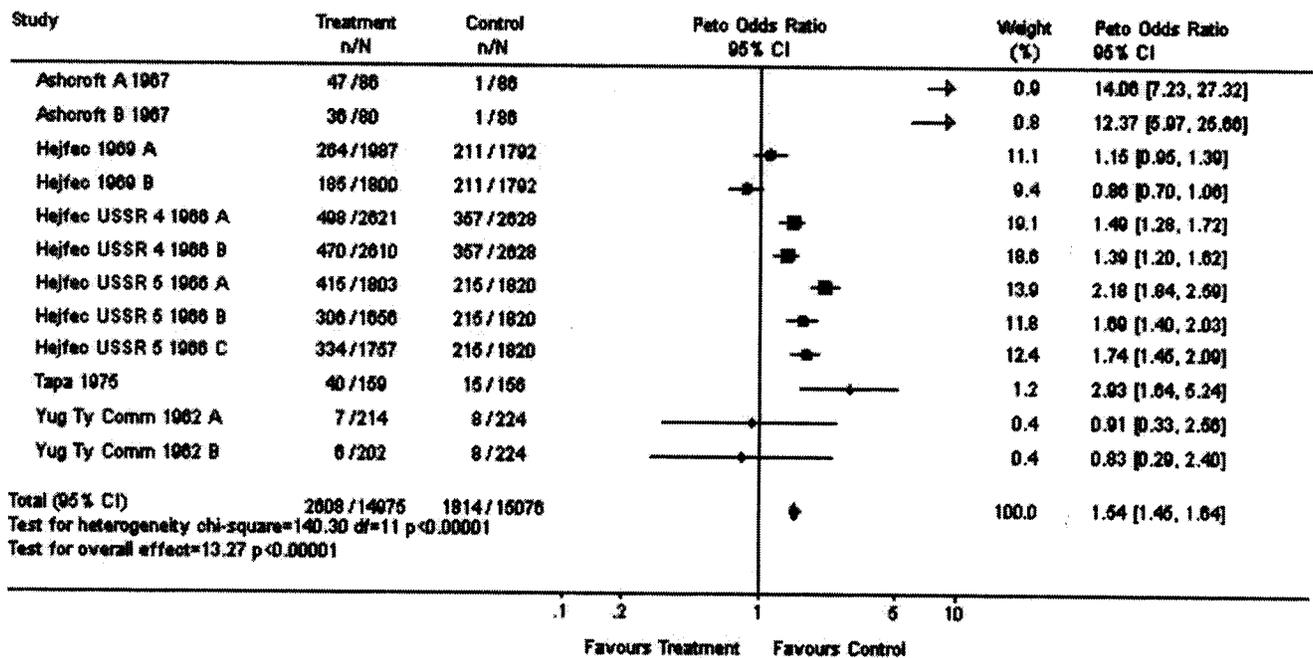
Review: Vaccines for preventing typhoid fever
 Comparison: 05 Ty21a vaccine vs. control: toxicity
 Outcome: 03 Diarrhea



Review: Vaccines for preventing typhoid fever
 Comparison: 06 Whole cell vaccines vs. control: toxicity
 Outcome: 01 Fever



Review: Vaccines for preventing typhoid fever
 Comparison: 06 Whole cell vaccines vs. control: toxicity
 Outcome: 02 Swelling



Review: Vaccines for preventing typhoid fever
 Comparison: 06 Whole cell vaccines vs. control: toxicity
 Outcome: 03 Missed school or work

