Vaccines for preventing typhoid fever (Review)

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[Intervention Review]

Vaccines for preventing typhoid fever

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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.

Authors' 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.

PLAIN LANGUAGE SUMMARY

Synopsis pending

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 physicans 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.

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;[Ferreccio 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.

AUTHORS' 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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