Typhoid fever vaccines: a meta-analysis of studies on efficacy and toxicity

Eric A Engels, Matthew E Falagas, Joseph Lau, Michael L Bennish

Division of Clinical Care Research, Department of Medicine, New England Medical Center, Tufts University School of Medicine, Box 63, 750 Washington Street, Boston, MA 02111, USA

Eric A Engels, *research fellow*

Tupper Research Institute, Division of Geographic Medicine and Infectious Diseases, Department of Medicine, New England Medical Center, Tufts University School of Medicine

Matthew E Falagas, *research fellow*

Michael L Bennish, *associate professor*

Division of Clinical Care Research, Department of Medicine, New England Medical Center, Tufts University School of Medicine

Joseph Lau, *associate professor*

Correspondence to: Dr Engels eric.engels@es.nemc.org

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Abstract

Objective: To estimate the efficacy and toxicity of typhoid fever vaccines.

Design: Meta-analysis of randomised efficacy trials and both randomised and non-randomised toxicity studies of the parenteral whole cell, oral Ty21a, and parenteral Vi vaccines.

Subjects: 1 866 951 subjects in 17 efficacy trials; 11 204 subjects in 20 toxicity studies.

Main outcome measures: Pooled estimates of three year cumulative efficacy, year specific efficacy, and incidence of adverse events.

Results: Three year cumulative efficacy was 73% (95% confidence interval 65% to 80%) for two doses of whole cell vaccines (based on seven trials); 51% (35% to 63%) for three doses of Ty21a vaccine (four trials); and 55% (30% to 71%) for one dose of Vi vaccine (one trial). For whole cell and Ty21a vaccines, regimens of fewer doses were less effective. Efficacy was shown to be significant for five years for whole cell vaccines, four years for Ty21a vaccine, and two years for Vi vaccine. Neither the age of vaccine recipient nor the incidence of typhoid fever in the control group (varying from 6 to 810 cases per 100 000 person years) affected the efficacy of the whole cell or Ty21a vaccines. After vaccination, fever occurred in 15.7% (11.5% to 21.2%) of whole cell vaccine recipients, 2.0% (0.7% to 5.3%) of Ty21a vaccine recipients, and 1.1% (0.1% to 12.3%) of Vi vaccine recipients.

Conclusions: Whole cell vaccines are more effective than the Ty21a and Vi vaccines but are more frequently associated with adverse events. Whether the added efficacy of the whole cell vaccines outweighs their toxicity will depend on the setting in which vaccination is used.

Introduction

Typhoid fever remains a substantial public health problem in developing countries. Each year 33 million people become ill and over 500 000 people die of this infection.[1] Typhoid is rare in industrialised nations, though travellers to endemic countries may occasionally acquire the disease.[2]

The interest in vaccines to prevent this disease is long standing. In 1904 the statistician Karl Pearson (in what may have been the first published meta-analysis on any topic[3]) reviewed seven studies of a heat inactivated typhoid vaccine conducted in British army units.[4] He concluded that these vaccine studies were flawed and that taken together they failed to show the efficacy of the vaccine. Despite Pearson's assessment and concerns about toxicity, this vaccine was later routinely used in the British army.

Since the first report, in 1962, of a randomised controlled trial of a typhoid vaccine,[5] 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.[6 7] Two vaccines developed more recently, Ty21a (an attenuated strain of *S typhi* administered orally) and Vi (the purified bacterial capsule, given parenterally), have seemed less toxic than the older whole cell vaccines and are thought to be equally effective.[2 8]

Whether any of the available vaccines would be useful in typhoid prevention in the developing world remains uncertain.[9] 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 the age of those vaccinated and their risk of acquiring typhoid fever, have not been systematically assessed.

In industrialised countries doctors may have to advise travellers on their risk of acquiring typhoid and ways to reduce that risk. Indeed, though typhoid vaccines were initially evaluated in populations living in endemic regions, today the vaccines are used mainly for travellers. One third of travellers presenting to doctors for advice are vaccinated.[10] Most are unlikely to develop typhoid; those at highest risk include travellers making prolonged visits to remote areas of endemic nations.[2]

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

Methods

Literature search and inclusion and exclusion criteria

To identify published efficacy trials of typhoid vaccines we conducted a literature search of the Medline database from 1966 to 1996. In the search we used the textwords "Salmonella," "salmonellosis," "typhoid," and "vaccine." We also conducted searches of *Index Medicus* (1955-66), Embase, and *The Cochrane Library* database.[11] We obtained additional studies from reference lists of retrieved articles and included studies in any language.

We included only field trials that reported the number of cases of typhoid fever in each arm of the trial. Included trials had control arms in which subjects received either placebo or a vaccine against a disease other than typhoid fever. We grouped vaccines included in this analysis into three 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).

Data extraction

From each trial report we extracted the vaccine formulation and the number of doses, age of subjects, duration of follow up, number of subjects, and number of cases of typhoid fever. In all trials the primary means of diagnosing cases of typhoid was isolation of *S typhi* from cultured blood, but five trials also included cases documented by stool, urine, or duodenal fluid cultures.[12–16] We noted whether randomisation was adequately described (description of unit of randomisation and method of generating random assignment); whether trial assignment was concealed from investigators; whether diagnosis of typhoid fever occurred blinded to assignment; whether surveillance for cases was active (staff 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). Two of the authors independently extracted these data; discrepancies were resolved through consensus discussions.

Analysis of vaccine efficacy

Published trials provided efficacy data for regimens with different numbers of doses and after various durations of follow up. For the primary analysis we examined the cumulative efficacy for 2.5-3 years of follow up for regimens with three doses of Ty21a, one dose of Vi, or two doses of whole cell vaccines. We chose these dose regimens because they were (*a*) the highest dose regimens for which trials presented data on these vaccines and (*b*) the regimens commonly used in practice. We chose 2.5-3 years of follow up because this was the longest time for which most studies provided data. For each intervention arm of the trials we calculated the incidence of typhoid fever per person year and an incidence ratio (incidence in the intervention arm divided by incidence in the control arm). We calculated these incidences based on any-dose data, but if these were unavailable we used all-dose data. For trials that compared several intervention arms with a single control arm we divided the control arm into equal portions so that we could pool the incidence ratios without counting control subjects more than once. We also separately examined efficacy for different formulations of the Ty21a and whole cell vaccines.

We combined the incidence ratios from each trial using a random effects model, an application[17] of the DerSimmonian-Laird method.[18] We report efficacy estimates and 95% confidence intervals as relative risk reductions (1 minus the pooled incidence ratio, expressed as a percentage). Efficacy was considered significant if the confidence interval did not contain zero.

Analysis of variables influencing efficacy

For each vaccine class, we separately pooled trial data for each year of follow up and for regimens with different numbers of doses. This allowed us to determine the duration of efficacy and the impact of number of doses on efficacy. For trials reporting data for only part of a year, we rounded duration of follow up to the closest year when deciding for which year of follow up the data would be used.

Some trials of Ty21a and whole cell vaccines also provided age specific data. To examine vaccine efficacy for subjects of different ages, we chose age cut offs that maximised the number of trials providing data for the resulting age subgroups. We then pooled the individual trials' efficacy estimates separately for these age subgroups.

Because the efficacy of an intervention may depend on a population's disease risk, and because the incidence of disease in the control group (the control incidence) is a measure of the trial population's risk of disease,[19] we examined the relation between trial control incidence and vaccine efficacy. For Ty21a and the whole cell vaccines we performed a weighted least squares linear regression of incidence ratio (log transformed) as a function of the trial's control incidence; we could not do this with the Vi vaccine because only one trial provided data at three years of follow up. For weights in the regression we used: 1/variance estimate for the natural logarithm of the incidence ratio.[20] Results are reported as confidence intervals for the regression line slope.

Analysis of vaccine toxicity

Many trials identified for our efficacy analysis did not provide information on adverse events that were associated with the vaccine; we therefore included non-randomised trials and cohort studies in our analysis of vaccine toxicity. We included only studies that used active surveillance for adverse events, and for the whole cell vaccines we restricted our analysis to the currently available heat inactivated vaccine. Because toxicity studies published in languages other than English tended to be small and difficult to obtain, we included only studies in English.

For each study we noted whether it was clinic based or field based, and we recorded the incidence after vaccination of fever, missed work, swelling at the injection site (Vi or whole cell vaccine), and vomiting and diarrhoea (Ty21a vaccine). We used a random effects model to pool logit-transformed estimates of the incidence of these outcomes among vaccine recipients.[18] For studies that reported toxicity on a "per dose" basis for multidose regimens (instead of "per subject") we counted each dose as a separate subject for pooled estimates.[6 21–26]

Results

Trials of vaccine efficacy

The 17 trials in this meta-analysis included 1 866 951 subjects (table 1). There were 5 trials of Ty21a (326 689 subjects; 11 vaccine arms),[13 14 27–29] 2 trials of Vi (17 822; 2),[30 31] and 10 trials of whole cell vaccines (1 522 440; 21).[5 7 12 15 16 32–35] The trials of Ty21a and Vi vaccines used either active or intermediate surveillance; the trials of the whole cell vaccines used passive surveillance (3 trials) or did not describe the surveillance (7). All the trials used some method of concealing the assignment status of subjects, but only 8 trial reports described both randomisation and blinding. Only 3 of 13 trials

Table 1 Efficacy trials of typhoid vaccines

Study	Country, year	Study design and reporting*				Age range (years)	Follow up (years)	Control incidence†	Arm and vaccine formulation/dose interval (days)	No of doses	No of subjects	Efficacy (95% CI)
		Dose	Surveillance	Randomisation	Blinding							
Ty21a vaccine:												
Wahdan et al[28]	Egypt, 1982	Any	Intermediate	Yes	Yes	6 to 7	3.0	46	Liquid/2	3	16 486	96 (67 to 99)
Levine et al[13]	Chile, 1987	All	Intermediate	No‡	Yes	6 to 21	3.0	104	A: enteric capsule/21	3	21 598	49 (23 to 66)
									B: enteric capsule/2	3	22 170	67 (46 to 79)
									C: gel capsule/21	3	21 541	31 (0 to 53)
									D: gel capsule/2	3	22 379	19 (–15 to 43)
Levine et al[14]	Chile, 1990	All	Intermediate	No‡	Yes	5 to 19	3.0	91	A: liquid/2	3	36 623	77 (60 to 87)
									B: enteric capsule/2	3	34 696	33 (–4 to 57)
Black et al[29]	Chile, 1990	All	Intermediate	No‡	Yes	5 to 22	5.0	120	A: enteric capsule/7	2	27 620	43 (26 to 56)
									B: enteric capsule	1	27 618	16 (–6 to 33)
Simanjuntak et al[27]	Indonesia, 1991	All	Intermediate	No	No	3 to 44	2.5	810	A: liquid/7	3	5 066	53 (36 to 66)
									B: enteric capsule/7	3	5 209	42 (23 to 57)
Vi vaccine:												
Acharya et al[30]	Nepal, 1987	Any	Active	Yes	No	5 to 44	1.4	655	Not applicable	1	3 457	72 (41 to 87)
Klugman et al[31]	South Africa, 1996	Any	Active	Yes	Yes	5 to 16	3.0	387	Not applicable	1	5 692	55 (30 to 71)
Whole cell vaccines:												
YTC[5]	Yugoslavia, 1962	All	Passive	Yes	No	5 to 50	6.0	77	A: heat/21	2§	11 503	72 (50 to 84)
									B: alcohol/21	2§	12 017	42 (10 to 62)
YTC[7]	Yugoslavia, 1964	All	Passive	Yes	No	2 to 60	2.5	595	A: heat/28	2	5 068	51 (27 to 67)
									B: acetone/28	2	5 028	79 (63 to 88)
Hejfec[32]	USSR, 1965	All	ND	Yes	Yes	7 to ?	0.7	256	Alcohol/20-30	2	22 269	37 (–5 to 62)
Hejfec et al[33] (USSR 4)	USSR, 1966	All	ND	Yes	Yes	7 to 18	2.5	77	A: heat/20-30	2	45 187	82 (69 to 89)
									B: alcohol/20-30	2	45 594	54 (34 to 69)
Hejfec et al[33] (USSR 5)	USSR, 1966	All	ND	Yes	Yes	7 to ?	2.5	62	A: heat/20-30††	2	45 213	86 (72 to 93)
									B: heat/20-30††	2	36 112	66 (43 to 79)
									C: alcohol/20-30	2	45 298	73 (55 to 84)
PTC[15]	Poland, 1966	Any	ND	Yes	No	5 to 60	3.0	16¶	A: acetone/28††	2	90 670	84 (64 to 93)
								6¶	B: acetone/28††	2	116 858	71 (28 to 88)
								10¶	C: formol/28	2	94 290	77 (60 to 87)
Ashcroft et al[12]	Guyana, 1967	Any	Passive	Yes	Yes	5 to 15	7.0	70	A: heat/35	2	26 802	67 (54 to 77)
									B: acetone/35	2	27 365	89 (81 to 93)
Hejfec et al[34]	USSR, 1968	Any	ND	Yes	Yes	7 to 16	2.5	56¶	A: heat††	1	20 832	73 (40 to 88)
								33¶	B: heat††	1	68 214	49 (20 to 67)
Hejfec et al[35]	USSR, 1969	Any	ND	Yes	No	7 to 20	1.8	48	A: acetone	1	52 347	51 (8 to 74)
									B: heat	1	52 698	59 (19 to 79)
Tapa et al[16]	Tonga, 1975	All	ND	No	Yes	2 to 60	7.5	64	A: acetone/28	2	11 128	40 (6 to 61)
									B: acetone/28	1	11 391	–5 (–53 to 28)

YTC=Yugoslav Typhoid Commission. PTC=Polish Typhoid Committee. ND=not described in study.
*Dose: any=data based on subjects getting at least one dose, all=data based only on subjects getting all doses; randomisation and blinding: yes=described, no=not described.
†Cases of typhoid per 100 000 person years in the control group.
‡Subjects were randomised by classroom; the method of generating random assignment was not described.
§About 75% of subjects in each arm received a third dose as a booster after one year of follow up.
¶Compared each intervention arm with a separate control arm.
††Compared different formulations of heat inactivated or acetone inactivated vaccines.

examining multidose regimens reported data on an any-dose basis.

Estimates of vaccine efficacy

The cumulative three year efficacy of two doses of the whole cell vaccines was 73%, of three doses of Ty21a was 51%, and of Vi vaccine 55% was effective (only one trial provided cumulative data for up to 3 years) (figure).

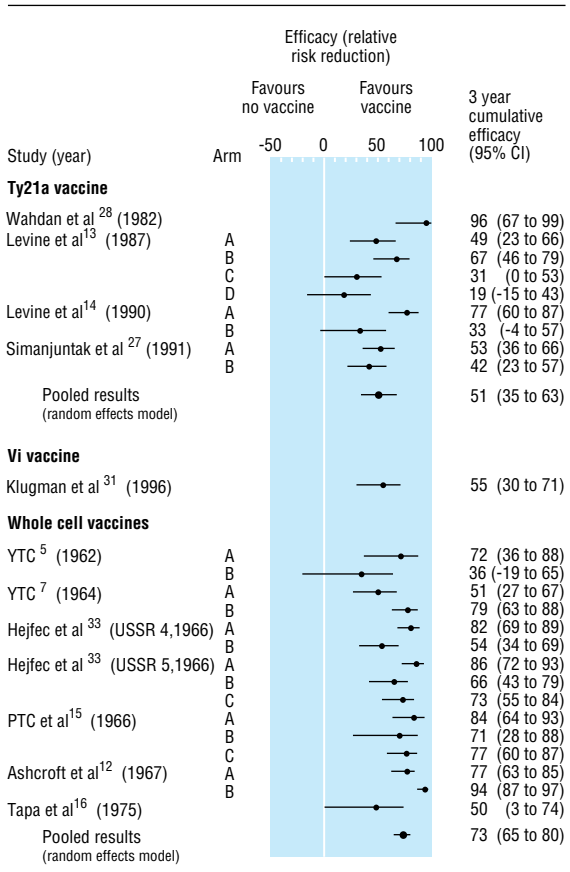
For Ty21a vaccine the efficacy of the liquid formulation was 74% (41% to 89%; 3 trials), of the enteric capsules was 47% (32% to 59%; 3), and of the gelatin capsules was 25% (−2% to 45%; 1). For the whole cell vaccines, the efficacy of acetone inactivated vaccine was 80% (61% to 90%; 4), of formol inactivated vaccine was 77% (60% to 87%; 1), of heat inactivated vaccine was 73% (61% to 82%; 5), and of alcohol inactivated vaccine was 58% (34% to 73%; 3).

Number of doses and duration of follow up

Table 2 shows the efficacy estimates for specific years of follow up and for varying numbers of doses. Some estimates for Ty21a and Vi vaccine regimens were based on few study arms or subjects.

For the whole cell vaccines, one dose regimens provided significant protection in each of the first two years, and two dose regimens provided significant protection in each of the first five years. Protection provided by two dose regimens was not significant in the sixth and seventh years.[5 12 16]

For the Ty21a vaccine, both two and three dose regimens provided significant protection in each of the



Estimates of three year cumulative efficacy from individual trials (see table 1) and pooled estimates, presented as relative risk reductions (percentages). Individual trial estimates are from arms that provided cumulative data for 2.5-3 years of follow up, for regimens with the following numbers of doses: three doses for Ty21a vaccine, one dose for Vi vaccine, and two doses for whole cell vaccines. YTC=Yugoslav Typhoid Commission; PTC=Polish Typhoid Committee

first two years. The three dose regimen provided significant protection in the third and fourth years but not in the fifth year. Data for efficacy of three doses of the Ty21a vaccine in the fourth and fifth years were from two reports[36 37] that presented extended follow up data for a single arm of a four arm trial[13]; this arm had shown the greatest efficacy at the end of the first three years, but no follow up data were presented for the three less effective arms.

The Vi vaccine provided significant protection in each of the first two years after vaccination. The protection in the third year was similar to that in the second year but was not significant. No efficacy data were published beyond three years' follow up.

Effect of age and control incidence on efficacy of vaccines

Efficacy was 80% (69% to 87%) for ages 2-18 years and 62% (30% to 79%) for ages 15-60 for the whole cell vaccines[7 12 15 33] and 71% (27% to 89%) for ages 5-9 and 63% (46% to 75%) for ages 10-44 years for the Ty21a vaccine.[13 14 27 28] The estimates for the Ty21a vaccine are higher than the overall efficacy estimate (51%) because one study presented no age specific data for the three trial arms with lowest efficacy.[13]

Wide confidence intervals for the linear regression slopes preclude any statement about the relation between efficacy and control incidence. The regression slope was 6.3 (−40 to 53) for the Ty21a vaccine and 51 (−24 to 126) for the whole cell vaccines.

Vaccine toxicity

We identified 20 studies providing toxicity data for 11 204 subjects (table 3). Fever occurred after vaccine administration more often with whole cell vaccine than with Ty21a or Vi vaccines. Swelling at the injection site also occurred more often with the whole cell than the Vi vaccine. Ty21a vaccine was associated with a 2.1% incidence of vomiting and a 5.1% incidence of

Table 2 Percentage (95% confidence interval) efficacy of typhoid vaccines by number of doses and year of follow up

Vaccine	Year 1	Year 2	Year 3	Year 4	Year 5
Ty21a					
One dose:					
Efficacy	25 (–9 to 49)	35 (–8 to 61)	1 (–87 to 48)	–6 (–77 to 37)	–10 (–113 to 43)
Patients (No of arms)	27 618 (1)	27 618 (1)	27 618 (1)	27 618 (1)	27 618 (1)
Two doses:					
Efficacy	52 (24 to 69)	71 (44 to 85)	22 (–54 to 60)	19 (–41 to 53)	7 (–84 to 53)
Patients (No of arms)	27 620 (1)	27 620 (1)	27 620 (1)	27 620 (1)	27 620 (1)
Three doses:					
Efficacy	50 (18 to 69)	60 (44 to 71)	60 (35 to 76)	78 (35 to 93)	47 (–24 to 78)
Patients (No of arms)	48 931 (4)	48 931 (4)	48 931 (4)	22 170 (1)*	22 170 (1)*
Vi					
One dose:					
Efficacy	67 (44 to 81)	52 (4 to 76)	50 (–11 to 78)	No data	No data
Patients (No of arms)	9149 (2)	5692 (1)	5692 (1)		
Whole cell					
One dose†:					
Efficacy	65 (49 to 76)	51 (6 to 74)	71 (–5 to 92)	37 (–98 to 80)	79 (44 to 92)
Patients (No of arms)	290 780 (11)	132 692 (9)	96 689 (7)	18 081 (3)	18 081 (3)
Two doses:					
Efficacy	74 (62 to 82)	72 (56 to 82)	74 (50 to 87)	73 (42 to 87)	67 (43 to 80)
Patients (No of arms)	663 491 (15)	406 310 (9)	406 310 (9)	64 617 (5)	64 617 (5)

The number of patients represents the total number of patients in trial intervention arms providing year specific and dose specific data; the number of arms represents the number of trial intervention arms providing data.
*Data are from Levine et al.[36 37]
†Some data come from studies reporting cases of typhoid in subjects who were randomised to, but failed to complete, two dose regimens.

Table 3 Toxicity studies of typhoid vaccines

Study	Age range (years)	Type of study	No of subjects vaccinated	Fever (%)	Swelling (%)	Vomiting (%)	Diarrhoea (%)	Missed school or work (%)
Ty21a vaccine:								
Gilman et al[38]	Adults	Clinic	155	1	NA	3	10	ND
Murphy et al[39]	0.5-2	Clinic	18	11	NA	17	11	ND
Rahman et al[40]	3-78	Clinic	157	2	NA	0	1	ND
Cryz et al[41]	2-6	Clinic	317	< 1	NA	1	< 1	ND
Cryz et al[21]	16-56	Clinic	30	2	NA	0	20	ND
Pooled estimate (95% CI)				2.0 (0.7 to 5.3)		2.1 (0.6 to 7.8)	5.1 (1.7 to 14.5)	
Vi vaccine:								
Levin et al[42]	ND	Clinic	21	24	ND	NA	NA	ND
Tacket et al[44]	20-24	Clinic	19	0	ND	NA	NA	0
Klugman et al[43]	5-15	Field	253	< 1	4	NA	NA	ND
Cumberland et al[22]	18-22	Clinic	388	< 1	1	NA	NA	ND
Mirza et al[45]	5-15	Field	435	0	8	NA	NA	ND
Pooled estimate (95% CI)				1.1 (0.1 to 12.3)	3.7 (1.3 to 9.6)			0 (not defined)
Whole cell vaccine (heat inactivated):								
YTC[23]*	5-50	Field	214	9	5	NA	NA	11
Ashcroft et al[6]*	5-15	Field	193	13	61	NA	NA	14
YTC[7]*	NA	Field	66	29	ND	NA	NA	17
Hejfec et al[32]	7-18	Field	2621	30	19	NA	NA	ND
Hejfec et al[33]	ND	Field	3463	26	21	NA	NA	ND
Hejfec et al[35]	7-20	Field	2157	13	13	NA	NA	ND
Dimache et al[24]	16-18	Field	94	27	ND	NA	NA	ND
Dimache et al[25]	21	Clinic	113	1	ND	NA	NA	ND
Dimache[26]	20	Field	100	34	ND	NA	NA	2
Cumberland et al[22]	18-22	Clinic	390	2	20	NA	NA	ND
Pooled estimate (95% CI)				15.7 (11.5 to 21.2)	20.0 (12.9 to 29.7)			10.0 (6.0 to 16.2)

YTC=Yugoslav Typhoid Commission.
NA-not applicable.
ND=not described in study.
*Provided estimates of incidence of adverse events at different time points without providing data on overall incidence. Data presented correspond to incidence at 24 hours after vaccination.

diarrhoea. Ten per cent of subjects missed school or work after receiving the whole cell vaccine; only one study of the newer vaccines specifically commented on this outcome.

Discussion

In this meta-analysis the three year efficacy of the whole cell vaccines exceeded the efficacy of the Ty21a vaccine. Although individual trial estimates varied widely for two doses of the inactivated whole cell vaccines and three doses of Ty21a, the pooled estimates from this study were associated with much narrower confidence intervals. The efficacy estimate for the Vi vaccine, though imprecise, was similar to the estimate for the Ty21a vaccine.

In the absence of trials directly comparing typhoid vaccines, this analysis of controlled trials provides the most valid means of assessing such vaccines, and it delineates the efficacy of these vaccines more precisely than previous qualitative reviews, which have tended to equate their efficacy.[2 8] When each year of follow up was examined separately the whole cell vaccines provided significant protection for five years, Ty21a vaccine for four years, and Vi vaccine for two years. With regimens using fewer doses of the whole cell and Ty21a vaccines, protection did not last as long as with regimens of standard numbers of doses.

The superior efficacy of the whole cell vaccines must be weighed against their higher incidence of adverse events. The incidence of fever with these vaccines was notably higher than with the Ty21a and Vi vaccines. A further indication of the toxicity of the whole cell (heat inactivated) vaccines is that 10% of individuals missed school or work after vaccination. This study supports a general clinical impression that the newer vaccines are associated with much lower toxicity than the whole cell vaccines.

Vaccination programmes for nations where typhoid is endemic

Whether a routine vaccination programme 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[27]—is a complex issue. The effectiveness of these vaccines in public health practice will be different from the efficacy noted in field trials, as the result of a vaccination programme depends on additional factors that influence immunity at population level ("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.[46]

Herd immunity may have a role in the epidemiology of typhoid fever. A typhoid control programme in Thailand, based in part on use of a heat inactivated vaccine, resulted in a 10-fold decrease in rates of

disease over eight years in all examined age groups, despite vaccination only of school age children.[47] The number of cases of paratyphoid fever remained unchanged, suggesting that the widely based decrease in cases of typhoid could be attributed to immunisation 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 trials of Ty21a vaccine in neighbouring areas.[48]

The relatively precise estimates of efficacy and toxicity that this study provides can be used to model the potential impact of a vaccination programme in nations where typhoid is endemic. We did not find a relation between vaccine efficacy and an individual's risk of disease (as reflected by control incidences varying from 6 to 810 cases per 100 000 population per year) or between efficacy and age (though we were limited by incomplete reporting of age specific data). Because the whole cell vaccines provide the greatest protection for the longest duration, these vaccines may be best suited among available vaccines for control programmes. The decision regarding which vaccine, if any, would be appropriate for typhoid control in endemic nations depends on a careful weighing of the benefits of vaccination and the side effects and costs. Currently none of the typhoid vaccines is administered as part of the World Health Organisation's expanded programme on immunisation, which targets children aged under 1 year.

The conclusions of this meta-analysis should also be interpreted in the context of variations in dose and formulation of Ty21a vaccine. Whereas Ty21a vaccine is available in most countries as a three dose regimen of enteric coated capsules, it is licensed for administration to travellers in the United States and Canada as a four dose series. A three year Chilean trial reported that four doses of the Ty21a vaccine is 40% more effective than three doses[49]; we did not include this study in our meta-analysis because it lacked a suitable control arm. Furthermore, our analysis suggests that the liquid formulation of Ty21a vaccine may be more effective than the enteric capsule formulation[14 27 28]; this liquid formulation is only now becoming commercially available. No data have been published examining whether four doses of any formulation of Ty21a vaccine provides protection for longer than three years.

Vaccination for travellers

Further research is needed to determine the efficacy of these vaccines in travellers to countries where typhoid is endemic. Though the overall incidence of disease in such travellers is low (<20 per 100 000), higher risk travellers constitute an important target group for typhoid vaccines.[2 9] None of the trials in this study examined this population, and it is not clear whether efficacy for travellers can be extrapolated from efficacy of vaccines in endemic countries, where individuals may already have some baseline immunity due to unapparent infections.[50] A single case-control study of travellers to India estimated the efficacy of the Ty21a vaccine to be 23%,[51] considerably lower than our estimate for populations living in countries where typhoid is endemic.

Our study suggests that Vi vaccine might be an appropriate choice of vaccine for short term travellers: protection need not be prolonged, and the efficacy of this vaccine is similar to that of the whole cell vaccines during the first year after vaccination. Also, the Vi vaccine has lower toxicity than the whole cell vaccines. Similarly, four doses of Ty21a vaccine may be effective prophylaxis for travellers. Though typhoid vaccination of travellers may not be cost effective,[10] travellers may still opt for vaccination after discussing with their doctors the benefits and side effects.

The apparent efficacy of an intervention may vary with differences in trial design.[52] Only 8 of the 17 trials provided descriptions of both randomisation methods and blinding of treatment assignment during follow up. Because there were few trials in each vaccine class, we were unable to analyse 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.[53]

Whether the higher toxicity of whole cell vaccines compared with the Ty21a or Vi vaccines outweighs their added efficacy will likely depend on the setting in which the vaccine is administered. This analysis provides useful data for comparing these vaccines.

Key messages

- Typhoid fever is an important public health problem in the developing world, but the efficacy of currently available vaccines has remained uncertain
- This meta-analysis of 17 vaccine efficacy trials and 20 toxicity studies of the whole cell, Ty21a, and Vi typhoid vaccines showed that whole cell vaccines probably offer the greatest protection for the longest time
- These vaccines, however, were associated with higher toxicity than the Ty21a and Vi vaccines
- The decision about whether to vaccinate against typhoid fever—and which vaccine to use—depends on the individual setting
- Efficacy trials of vaccines should use standardised trial designs and methods of reporting

Contributors: EAE was the principal investigator for the study. He conceived of the study through discussions with MLB. EAE performed the literature search. EAE and MEF extracted the data. JL served as the expert on the design of the meta-analysis and the methods used. MLB served as the expert on vaccine use in developing countries, with special reference to typhoid fever. All four authors were involved in designing the study, analysing the data, and writing and reviewing drafts of the manuscript; EAE was the primary author of the manuscript. Michael D Aubert retrieved references, and Christopher H Schmid provided statistical advice. EAE and MLB are the guarantors.

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Retraction

First myocardial infarction in patients of Indian and European origin: comparison of risk factors, management, and long term outcome

The authors of this paper (N Shaukat, J Lear, A Lowy, S Fletcher, D P de Bono, K L Woods. *BMJ* 1997;314:550-4) have written: "Further examination of the data on which this paper was based, in the context of another project, has revealed important inaccuracies such that the conclusions of the paper cannot be sustained. We therefore wish to withdraw it unreservedly."

Corrections

Household survey of locomotor disability caused by poliomyelitis and landmines in Afghanistan

An error occurred in this paper by Lambert and colleagues (29 November, pp 1424-5). The footnote to the table should have read: 3 children had received an injection before the onset of paralysis and would not be included if WHO definition was strictly applied (not that 3 children received an injection of polio vaccine).

Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol

An error occurred in this paper by A Li Wan Po and W Y Zhang (13 December, pp 1565-71). Co-proxamol was incorrectly described as containing 650 mg paracetamol and 32.5 mg dextropropoxyphene hydrochloride. The third sentence of the introduction should have read: "Co-proxamol, a combination product containing 325 mg paracetamol and 32.5 mg dextropropoxyphene hydrochloride, was the most popular prescription, accounting for 35%.[1]"