Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China

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Objective To test the efficacy of locally produced Vi vaccine over a time period of longer than one year.
Methods A double-blinded, randomized field trial was performed in Guangxi Zhuang Autonomous Region in south-western China, using 30 μg doses of locally produced Vi. Enrolled subjects were 3–50 years of age, although the majority (92%) were school-aged children, who have the highest rate of typhoid fever in this setting. A total of 131 271 people were systematically allocated a single dose of 30 μg of Vi polysaccharide or saline placebo. The study population was followed for 19 months, with passive surveillance conducted in the Ministry of Health and the Regional Health and Anti-epidemic Centre (HAEC). Clinically suspected cases of typhoid fever were confirmed by blood culture, or by serological reaction with O-antigen (Widal tests).
Findings After 19 months, there were 23 culture-confirmed cases of typhoid fever in the placebo group versus 7 cases in the Vi group (Protective efficacy (PE) = 69%; 95% CI = 28%, 87%). Most of the isolates were from school-aged children: 22 cases in the placebo group versus 6 in the Vi group (PE = 72%; 95% CI = 32%, 82%). No serious post-injection reactions were observed. The locally produced Vi polysaccharide vaccine showed levels of protective efficacy similar to those for Vi vaccine produced in industrial countries.
Conclusion The slightly higher dose of vaccine did not seem to alter efficacy significantly in China.

Keyword Typhoid-paratyphoid vaccines/administration and dosage; Polysaccharides, Bacterial/immunology; Typhoid fever/immunology; Placebos; Clinical trials, Phase II; China (*source: MeSH*).

Mots clés Vaccin antityphoparatyphoïdique/administration et posologie; Polyosides bactériens/immunologie; Fièvre typhoïde/immunologie; Placebo; Essai clinique phase II; Chine (*source: INSERM*).

Palabras clave Vacunas tifoide-paratifoide/administración y dosificación; Polisacáridos bacterianos/inmunología; Fiebre tifoidea//inmunología; Placebos; Ensayos clínicos fase II; China (*fuente: BIREME*).

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Voir page 630 le résumé en français. En la página 630 figura un resumen en español.

Introduction

Typhoid fever is still an endemic infectious disease in some rural areas of China, especially in the south. The warm climate and the abundance of rice fields frequently promote outbreaks of the disease. For

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example, the annual typhoid incidence for school-aged children in Jiangsu and Guangxi provinces is approximately 50 cases per 100 000 population. The leading cause of enteric fever in many countries is *Salmonella typhi*, followed by *S. typhimurium* and *S. paratyphi*. The main factors contributing to endemic typhoid may be a lack of adequate sewage disposal and a lack of protected water supplies, and in many developed countries the provision of safe water supplies has controlled or even eliminated typhoid. In developing countries, however, national or international efforts to reduce typhoid by providing effective sewage treatment and clean water may be required for at least a decade. Thus, the intensive use of an effective and safe vaccine in developing countries, especially in children, will probably be necessary to reduce the incidence of typhoid fever in endemic areas.

In the 1980s, killed whole cell vaccine was used to control endemic typhoid. Although this vaccine was effective, its widespread use has been impeded by unpleasant local and systemic side-reactions. Since 1990, the National Institute for Control of Pharmaceutical and Biological Products (NICPBP) of China has organized six Institutes of Biological Products to study the production of an alternative vaccine against typhoid fever derived from Vi polysaccharide. In a pilot study, the safety and immunogenicity of Vi vaccine produced in China showed that it was effective and safe. A further field test of a single 30-μg dose of Vi vaccine in 81 000 people in Jiangsu Province demonstrated a protective efficacy of 71% after 12 months. As a result, the Vi polysaccharide vaccine was licensed as an experimental vaccine in China. However, to issue a formal production license in China the efficacy of the vaccine needed to be field tested over longer periods in other highly endemic areas. In this paper, we report the findings of a 19-month randomized, double-blinded field trial conducted in a predominantly school-aged group in Guangxi Province, in which we tested the efficacy of a single 30-μg dose of Vi polysaccharide vaccine.

Methods

Pilot study

A pilot study was conducted to compare the immunogenicity and safety of Vi polysaccharide vaccine with commercially produced, killed, whole cell typhoid vaccine. The study was performed in 585 students aged 15–20 years in Jiangsu Province (*1*). Participants were allocated to one of five groups, each of which received a single-dose regimen: group 1 (118 students) 20 μg Vi vaccine hypodermically; group 2 (116 students) 30 μg Vi vaccine hypodermically; group 3 (113 students) 30 μg Vi vaccine intramuscularly; group 4 (118 students) 1.5 E/0.5 ml killed whole cell typhoid vaccine hypodermically; group 5 (120 students) 0.5 ml normal saline delivered hypodermically.

In group 2 (the high dose Vi vaccine group), only 3% of the subjects developed fever (>37.5 °C), or local reactions (erythema >1cm), 24 hours after vaccination, and all symptoms resolved within 48 hours after vaccination. The geometric mean titre (GMT) of anti-Vi antibodies in group 2, assessed with enzyme-linked immunosorbent assay (ELISA), rose from 5.4 μg/ml pre-vaccination to 50.2 μg/ml one month after vaccination, and declined to 38.2 μg/ml six months after vaccination. Ninety-two percent of group 2 participants achieved a ⩾4fold rise of anti-Vi antibodies over baseline one month after vaccination. In contrast, only 81% of group 1 and 88% of group 3 participants achieved such antibody titres, and 29.4 μg/ml or 27.7 μg/ml of GMT six months after vaccination in group 1 and group 3. Consequently, a 30-μg dose of Vi vaccine was used hypodermically in the field trial conducted in Guangxi.

Main study in Guangxi

Setting

The trial was undertaken in the county of Quan, located in the north-eastern part of Guangxi Zhuang Autonomous Region, in southern China. The trial was approved by the Ministry of Health of China, by the Government of Quan County, and by the Health Bureau and Educational Bureau of Quan County. The total area covered was 4003 km^2, and included 20 townships. In the beginning of 1995, a census was conducted of all 20 townships targeted for the trial. The total population in 1995 was 767 046, of which 147 084 were school-aged children. It has been suggested that earlier typhoid fever outbreaks were caused by drinking unsanitary water during warm weather. The annual incidence from 1990 to 1994 was 63–78 per 100 000 population, and 25% of the cases were among school-aged children.

The public health system in Quan was organized in three tiers. In the first tier, county anti-epidemic centres (HAEC) were staffed with physicians, epidemiologists and microbiologists, and equipped with microbiology laboratories. The centres were responsible for the storage and dispensing of vaccines. In the second tier, township health centres (THC) were also staffed with physicians and nurses, and were equipped to store vaccines and blood samples temporarily. The health centres were also responsible for inoculation, surveillance and collecting blood samples. In the third tier, more than 400 health stations in villages were staffed with health workers trained to collect blood samples from suspected cases of typhoid fever. Schools were also provided with similar health stations during school hours. HAEC laboratories reconfirmed all suspected blood isolates.

Eligibility

Healthy children between 3 and 19 years old were recruited after obtaining signed informed consent from parents. In addition, approximately 10 000 adults up to the age of 50 years were recruited, of whom

6900 were workers from the public service system; the rest were health workers and teachers. All participated after giving signed informed consent. People with chronic disease, under medication, or pregnant were excluded from the study.

Vaccine and placebo

The Vi polysaccharide vaccine (lot # 941201) used in the trial was produced by the Shanghai Institute of Biological Products, according to WHO good management practice (GMP) criteria. The NICPBP confirmed that the quality of the vaccine met WHO requirements (WHO Technical Report Series No. 840, 1994). The vaccine was prepared in concentrations of 60 μg Vi vaccine/ml. The vaccine was stored at 4–8 °C prior to administration. Vaccination dates were between 3 and 22 March 1995 (the expiration date of the vaccine was December 1996). The placebo for the trial consisted of normal saline, distributed in vials identical in appearance to those used for the Vi vaccine.

Allocation to vaccine or placebo

All study participants were given a unique, consecutive serial number within their relevant group (e.g. classroom, working unit, etc.). The vaccine and placebo, coded as #941201 and #950101, respectively, were assigned to individuals according to whether the individual had an even or odd serial number. Both field workers and the study population were kept blinded to the identities of these codes, which were not broken until surveillance was complete and the data set for the outcome events was finalized.

Surveillance

Systemic and side reactions after injection were monitored passively for 48 hours by parental reports for students in three participating schools (one primary school, one junior middle school, and one senior middle school).

Cases of typhoid fever were detected by surveillance at one county HAEC, three county hospitals and 20 health centres at the township level. This surveillance was done for both inpatients and outpatients at the county and township level. A case of typhoid fever was defined as the onset of compatible clinical symptoms or signs more than four weeks after administration of the vaccine or placebo, together with the isolation of *S. typhi* from a blood culture. Compatible symptoms and signs of typhoid fever included: fever >38 °C for more than one day, malaise, anorexia, relative bradycardia and splenomegaly. A total of 3 ml of blood were collected and 1 ml was inoculated into glucose bile salt enrichment broth and screened for *S. typhi* by laboratories at Quan county HAEC, and confirmed by GHAEC. Isolates were identified with routine bacteriological techniques using SS and McConkey agar as selective media, and KIA (lactose-glucose iron agar) slope for biochemical reaction. All isolates were agglutinated by specific anti-sera. In addition, for patients with compatible symptoms of typhoid, paired sera were solicited at presentation and 2–4 weeks later. The sera were tested for agglutination with the O-antigen of *S. typhi* (Widal test). Paired sera exhibiting at least a 4fold rise in antibodies, or single sera with an anti-O titre $\geqslant$1:160, were classified as positive.

Analyses

Groups were compared for categorical variables by the χ^2 test or, when data were sparse, by Fisher's exact test. Continuous variables were compared by Student's t test. Vaccine protection was expressed as protective efficacy (PE), and calculated as [1 – (risk of typhoid in vaccinees/risk of typhoid in controls)] x 100. To provide confidence intervals for PE, test-based methods were used to estimate confidence intervals for relative risks. All *P*-values and confidence intervals were estimated in a two-tailed fashion.

Results

Of the 292 primary schools and 94 774 students in Quan county, we approached 245 of the schools (total, 80 558 students — 85% of the total student population). Some 5397 students refused to participate in the study and 31 students were judged ineligible. Of the 76 middle schools with 52 310 students, we approached 47 017 (90%) of the students in 62 schools. Some 2300 students refused to participate, and 26 students were judged ineligible. Among the 11 180 adults approached for the trial, 339 refused to participate and 15 were judged ineligible. In total, 65 287 subjects received Vi vaccine and 65 984 subjects received the saline placebo. In three participating schools, no serious vaccine reactions after injection were detected by passive surveillance for systemic and local side-effects. Only 0.5% of vaccinees were noted to have fever, with none developing temperatures >38.5 °C. Local reactions, including pain and erythema, were also noted in 0.5% of vaccinees. The Vi vaccine and placebo control groups were similar with respect to age, sex and profession (Table 1).

The results of the study are shown in Table 2. Of the 1123 blood cultures collected from residents who had clinical manifestations consistent with typhoid fever, 300 samples were collected by the county HAEC (with 15 samples (5%) being culture positive); 210 samples were collected by hospitals (with 12 samples (6%) being culture positive); and 613 samples were collected by the THCs (with 22 samples (4%) being culture positive). No significant differences in culture-positivity rates were detected in the three settings. In total, 37 strains of *S. typhi* and 12 strains of *S. paratyphi* A were isolated, with 30 strains of *S. typhi* and 9 strains of *S. paratyphi* A isolated from participants in the field trial.

During the 19 months of post-vaccination follow-up, 30 culture-confirmed cases of typhoid fever occurred among trial participants, 7 in the Vi

Table 1. **Characteristics of vaccinated and control groups**

Characteristic	Vi vaccinated group (%)[a]	Placebo control group (%)
Age at enrolment (years)		
3–4	302 (0.5%)[a]	309 (0.5%)
5–9	17 776 (27.2%)	18 386 (27.9%)
10–14	32 667 (50.0%)	32 662 (49.5%)
15–19	9 656 (14.8%)	9 727 (14.7%)
20–25	4 886 (7.5%)	4 900 (7.4%)
Primary school student	37 421 (57.3%)	37 709 (57.1%)
Middle school student	22 295 (34.2%)	22 666 (34.4%)
Government employee	2 160 (3.3%)	2168 (3.3%)
Worker	3 411 (5.2%)	3441 (5.2%)
Female	28 249 (43.3%)	28 276 (42.9%)
Total number of participants	**65 287**	**65 984 (42.9%)**

[a] Percentages are calculated from the total number of participants in the vaccinated group, or control group, as appropriate.

vaccine group and 23 in the control group (Table 3; PE = 69%; 95% CI = 28%, 87%, see ref. *2*). Based on the Widal test of paired serum for O-antibody 4fold rise, there were 20 positive cases, 5 from the Vi vaccine group and 15 from the control group (PE = 66%; 95% CI = 7%, 88%). Based on Widal test of single serum specimens demonstrating anti-O agglutinins $\geqslant$1:160, there were 50 positive cases, 12 from the Vi vaccine group and 38 from the control group (PE = 68%; 95% CI = 39%, 83%).

Table 4 shows the distribution of typhoid fever cases by age, sex, profession, body temperature at presentation, and duration of sickness. Most of the cases were among children 5–19 years old: 6 out of 7 occurred in the Vi vaccine group and 22 out of 23 occurred in the control group. The efficacy of the Vi vaccine in school-aged children was 72% (95% CI = 32%, 82%). Most typhoid cases were male, but levels of vaccine efficacy did not differ significantly between males and females. Typhoid cases among vaccinees and controls were equally severe, as measured by the presenting body temperature and duration of illness. In addition to typhoid fever, there were 9 cases of *S. paratyphi* A isolated in the target population, with equal risks in vaccinees (4 cases) and controls (5 cases).

Discussion

Typhoid is still a major health problem in many parts of the world, particularly in south-east Asia. Since the 1990s, the treatment of typhoid fever has become difficult due to the emergence of antibiotic-resistant strains (*3, 4*). With limited improvements in water quality and hygiene foreseeable in the short term for many typhoid-endemic areas of the developing world, immunization against typhoid has become an attractive public health option (*5, 6*).

In China typhoid has been most common in the southern provinces, where rice is the dominant crop and summer floods are common. An immunization programme against typhoid started in the 1980s. Both injectable killed whole cell and live orally administered (Ty21a) vaccines were used, but severe local side-effects were observed and the Ty21a vaccine had limited application due to its high cost. In 1990, the technology for producing Vi polysaccharide vaccine was introduced in China by scientists from the US National Institutes of Health. Since China had been producing a similar polysaccharide vaccine (meningococcal A capsular polysaccharide vaccine) for general immunization, and therefore had the technology to produce the Vi vaccine, the Ministry of Health authorized a joint research

Table 2. **Typhoid case reports in Quan county, 1995–96**

Month	1995				1996				
	No. cases reported	No. blood samples taken	No. cases due to *S. typhi*	No. cases anti-O positive[a]	No. cases reported	No. blood Samples taken	No. cases due to *S. typhi*	No. cases anti-O positive	No. cases due to *S. paratyphi A*
Jan	12	–	–	–	29	6	–	–	–
Feb	12	–	–	–	14	1	–	–	–
Mar	34	8	–	–	14	8	–	1	–
Apr	24	118	1	–	26	15	1	–	–
May	40	116	3	1	48	47	1	1	–
Jun	55	143	1	1	25	24	–	1	–
Jul	52	79	1	7	28	31	1	1	1
Aug	53	53	2	6	35	99	4		2
Sep	112	60	3	9	52	120	9	4	3
Oct	126	78	4	13	40	59	3	1	4
Nov	65	31	2	6	36	20	1	–	2
Dec	18	6	–	–	14	1	–	–	–
Total	**603**	**692**	**17**	**43**	**361**	**431**	**20**	**9**	**12**

[a] Participants were considered to be anti-O positive if the titre was 4-fold above baseline, or $\geqslant$ 1: 640.

programme among six Institutes of Biological Products for Vi vaccine production.

Our data demonstrate that the locally produced Vi vaccine conferred 69% protection against culture-confirmed typhoid fever. This level of protection is similar to that observed for Vi vaccine produced in industrialized countries and tested in both Nepal and South Africa (*7, 8*) and is also similar to the level of protection observed in the earlier field trial of locally produced Vi vaccine in Jiangsu Province (*9*). The slightly higher dose tested in the present trial (30 μg/dose) did not improve upon the protection observed earlier in Nepal and South Africa using a lower vaccine dose (25 μg/dose).

We believe that it is very unlikely that our findings could have arisen as a result of bias. The two treatment groups were comparable at baseline (Table 1). Moreover, the double-blinded conditions of the trial make it implausible that the apparent protection observed in the Vi vaccine group could have occurred because of a co-intervention in this group, such as better water-hygiene behaviour. Several observations argue against detection bias as an explanation. First, the population under study was stable, with very little outmigration during the study period. Moreover, the fact that the overwhelming majority of participants were students made it relatively easy for the monitoring physicians from the HAEC to detect suspected typhoid cases for evaluation. This detection process was further strengthened by payment of incentive fees to both patients and clinicians for each culture-proven typhoid case.

Second, among the 190 clinically suspected typhoid fever cases that lacked evidence of *S. typhi* by blood culture or Widal testing, approximately equal numbers occurred in the two treatment groups: 90 cases in the Vi vaccine group and 88 cases in the control group. Curiously, the preponderance of typhoid cases observed among males (Table 4) was also observed for cases lacking laboratory evidence of typhoid fever, even though the numbers of such cases for each gender were balanced by treatment group (there were 55 males and 35 females in the Vi vaccine group and 60 males and 28 females in the control group).

Third, among people receiving blood cultures, the mean time from onset of fever to presentation for care was similar for the two treatment groups (4.95 ± 3.33 days for the Vi vaccine group versus 4.75 ± 3.37 days for the control group). Finally, the similar distribution of *S. paratyphi* A cases in the two groups (4 cases in the Vi vaccine group versus 5 cases in the control group) also supports the absence of detection bias, since no vaccine protection was anticipated against this organism owing to the differing specificities of the surface antigens of *S. typhi* and *S. paratyphi* A.

According to the notification of communicable diseases, the annual incidence of typhoid fever in the total population, based on clinical examination (often without culture-confirmation), was 63–78 cases per 100 000 population in 1990–94; 79 cases per 100 000 population in 1995; and 47 cases per 100 000 population in 1996 (Table 2). For students, the average annual incidence in 1990–94 was 62 cases per 100 000 population. The annual incidence for the control group in 1995–96 was 72 cases per 100 000 population, for cases documented either by culture or Widal test. This is slightly higher than the routinely reported rates for 1990–94. However, the slight increase in 1995–96 for controls could be due to the fact that in the present rates may be contained some mild cases that have been confirmed by culture or by Widal tests for strengthening passive surveillance.

Based on the favourable results of the two Vi vaccine trials in China, Vi vaccine has been used routinely nationwide since July 1996. More than 10 million doses were distributed in 1997 in China, with 800 000 doses per year distributed in Guangxi

Table 3. **Efficacy of Vi polysaccharide typhoid vaccine 19 months after immunization**

	Vi vaccinated group	Placebo control group	Protective efficacy (PE) %	95% CI for PE %
No. blood culture positive cases	7	23	69	28, 87
No. cases with serum anti-O titre rise ⩾ 4-fold	5	15	66	7, 88
No. cases with serum anti-O ⩾ 1:1640	125	3817	7068	3920, 839
Total no. participants	**65 287**	**65 984**		

Table 4. **Distribution of blood culture proven cases of typhoid fever**

Distribution	Vi vaccinated group	Placebo control group	Protective efficacy (PE) %	95% CI for PE %
By age (years)				
3–4	0	0	–	–
5–9	2	4	46	0, 90
10–14	2	13	85	77, 97
15–19	2	5	60	0, 92
>20	1	1	0	–
By gender				
Female	1	5	80	0, 97
Male	6	18	66	15, 87
By profession				
Primary school	4	15	73	19, 91
Middle school	2	7	80	0, 94
Worker	1	1	0	–
Total No. cases	7	23	69	–
Mean presenting temperature (°C)[a]	39.6 ± 0.4	39.2 ± 0.8	–	–
Mean duration of sickness (days)[a]	19.8 ± 10.9	23.2 ± 10.1	–	–

province in 1996 and 1997. The implementation of Vi immunization in China includes vaccination in outbreak areas and general immunization in school-aged children. Efforts are under way to introduce a locally produced bivalent Vi-meningococcal A vaccine into public health practice. We are in the process of studying the safety and immunogenicity of this bivalent vaccine, which could be given to children at the time of their last scheduled mennigococcal A injection. ■

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Conflicts of interest: None declared.

Résumé

Essai d'efficacité du vaccin antityphoïdique polyosidique Vi dans le sud-ouest de la Chine

Objectif Tester l'efficacité du vaccin antityphoïdique polyosidique Vi de production locale sur une période de plus d'un an.

Méthodes Un essai de terrain randomisé en double aveugle a été réalisé dans la région autonome (province) de Guanxi Zhuang dans le sud-ouest de la Chine, au moyen de doses de 30 μg de polyoside Vi de production locale. Les sujets recrutés dans l'étude étaient âgés de 3 à 50 ans, mais étaient pour la plupart (92 %) des enfants d'âge scolaire, groupe qui présente le taux le plus élevé de fièvre typhoïde dans cette région. Au total, 131 271 personnes ont reçu systématiquement une dose unique de 30 μg de polyoside Vi ou un placebo (soluté physiologique). La population d'étude a été suivie pendant 19 mois dans le cadre d'une surveillance passive exercée par le Ministère de la Santé et le Centre régional de la santé et de la lutte contre les épidémies (HAEC). Les suspicions cliniques de fièvre typhoïde ont été confirmées par hémoculture ou par réaction sérologique en présence d'antigène O (test de Widal).

Résultats Au bout de 19 mois, on a dénombré 23 cas de fièvre typhoïde confirmés par culture dans le groupe placebo contre 7 cas dans le groupe Vi (efficacité protectrice (EP) = 69 % ; intervalle de confiance à 95 % (IC 95 %) : 28-87 %). La plupart des isolements ont été réalisés chez les enfants d'âge scolaire, avec 22 cas dans le groupe placebo contre 6 cas dans le groupe Vi (EP = 72 % ; IC 95 % : 32-82 %). Aucune réaction grave n'a été observée après l'injection. Le vaccin polyosidique Vi de production locale a montré des taux d'efficacité protectrice similaires à ceux des vaccins produits dans les pays industrialisés.

Conclusion La dose légèrement plus forte de vaccin n'a pas semblé modifier l'efficacité de façon significative en Chine.

Resumen

Ensayo de la eficacia de la vacuna antitifoídica basada en el polisacárido Vi en el suroeste de China

Objetivo Determinar la eficacia de la vacuna de Vi producida localmente a lo largo de un periodo superior a un año.

Métodos Se llevó a cabo un ensayo sobre el terreno aleatorizado y en doble ciego en la región autónoma (provincia) de Guangxi Zhuang, en el suroeste de China, usando dosis de 30 μg de la vacuna Vi producida localmente. El intervalo de edades de las personas participantes era de 3-50 años, si bien la mayoría de ellas (92%) eran niños en edad escolar, los más afectados por la fiebre tifoidea en ese lugar. Se asignó de forma sistemática a un total de 131 271 personas para que recibieran ya fuera una dosis única de 30 μg de polisacárido Vi o bien un placebo constituido por suero fisiológico. La población estudiada fue objeto de seguimiento durante 19 meses, y la vigilancia pasiva corrió a cargo del Ministerio de Salud y del Centro Regional de Salud y Lucha contra las Epidemias (HAEC). Los casos con manifestaciones clínicas sugestivas de fiebre tifoidea fueron confirmados mediante cultivo sanguíneo o mediante la reacción serológica con el antígeno O (pruebas de Widal).

Resultados Al cabo de 19 meses se habían confirmado mediante cultivo 23 casos de fiebre tifoidea en el grupo placebo, frente a 7 casos en el grupo tratado con la vacuna Vi (eficacia protectora (EP) = 69%; IC95% = 28–87%). La mayoría de los aislados correspondían a niños en edad escolar: 22 casos en el grupo placebo, frente a 6 en el grupo tratado con Vi (EP = 72%; IC95% = 32–82%). No se observó ninguna reacción grave postinyección. La vacuna basada en el polisacárido Vi producida localmente demostró tener una eficacia protectora similar a la de la vacuna Vi producida en los países industrializados.

Conclusión El ligero aumento de la dosis de vacuna no parece haber influido de forma significativa en su eficacia en China.

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