Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China

Ding Ding,[1] Paul E. Kilgore,[2] John D. Clemens,[3] Wei Liu,[4] & Zhi-Yi Xu[5]

Objective To assess the cost-effectiveness of inactivated and live attenuated Japanese encephalitis (JE) vaccines given to infants and children in Shanghai.

Methods A decision-analytical model was constructed in order to compare costs and outcomes for three hypothetical cohorts of 100 000 children followed from birth in 1997 to the age of 30 years who received either no JE vaccine, inactivated JE vaccine (P3), or live attenuated JE vaccine (SA 14-14-2). Cumulative incidences of JE from birth to 30 years of age in the pre-immunization era, i.e. before 1968, were used to estimate expected rates of JE in the absence of vaccination. The economic consequences were measured as cost per case, per death, and per disability-adjusted life year (DALY) averted for the two JE immunization programmes.

Findings In comparison with no JE immunization, a programme using the P3 vaccine would prevent 420 JE cases and 105 JE deaths and would save 6456 DALYs per 100 000 persons; the use of the SA 14-14-2 vaccine would prevent 427 cases and 107 deaths and would save 6556 DALYs per 100 000 persons. Both kinds of immunization were cost saving but the SA 14-14-2 vaccine strategy resulted in a saving that was 47% greater (US$ 512 456) than that obtained with the P3 vaccine strategy (US$ 348 246).

Conclusion Both JE immunization strategies resulted in cost savings in comparison with no JE immunization. This provides a strong economic rationale for vaccinating against JE in Shanghai and suggests that vaccination against JE might be economically justifiable in other parts of China and in certain other developing countries of Asia where the disease is endemic.

Keywords Japanese encephalitis vaccines/pharmacology; Vaccines, Attenuated/pharmacology; Vaccines, Inactivated/pharmacology; Immunization programs/economics; Cost of illness; Cost savings; Cost-benefit analysis; Cohort studies; Comparative study; China (*source: MeSH, NLM*).

Mots clés Vaccins antiencéphalite japonaise/pharmacologie; Vaccin atténué/pharmacologie; Vaccin inactivé/pharmacologie; Programmes de vaccination/économie; Coût maladie; Réduction coût; Analyse coût bénéfice; Etude cohorte; Etude comparative; Chine (*source: MeSH, BIREME*).

Palabras clave Vacunas contra la encefalitis japonesa/farmacología; Vacunas atenuadas/farmacología; Vacunas inactivadas/farmacología; Programas de inmunización/economía; Costo de la enfermedad; Ahorro de costo; Análisis de costo-beneficio; Estudios de cohortes; Estudio comparativo; China (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: لقاحات التهاب الدماغ الياباني، فارماكولوجيا لقاحات التهاب الدماغ الياباني، اللقاحات الموهَّنة، فارماكولوجيا اللقاحات الموهَّنة، اللقاحات المعطَّلة، فارماكولوجيا اللقاحات المعطَّلة، برامج التمنيع، اقتصاد برامج التمنيع، تكاليف المرض، توفير التكاليف، تحليل التكاليف والمنافع، دراسات الأتراب، دراسة مقارنة، الصين (*المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لإقليم شرق المتوسط*).

Bulletin of the World Health Organization 2003;81:334-342.

Voir page 341 le résumé en français. En la página 341 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية على الصفحة ٣٤٢.

Introduction

Japanese encephalitis (JE), a mosquito-borne viral infection, remains a major public health problem in Asia, reportedly causing 16 000 to 50 000 acute encephalitic episodes and 5000 to 10 000 deaths annually. The syndromes caused by the virus range from encephalomyelitis to mild febrile illness. Where JE is endemic it is principally a disease of children, the highest rates occurring in children aged under 10 years living in rural areas, especially where rice is grown and pigs are reared (*1*). Furthermore, long-term neurological disability occurs in an appreciable fraction of JE survivors (*2*).

In Japan and the Republic of Korea, national programmes of routine immunization with inactivated JE vaccine derived from mouse brain have nearly eliminated the disease, even in the areas of highest risk (*1*). Since 1968, JE vaccines have been provided for certain populations at high risk in China. Early success in controlling the disease in China was achieved by means of an inactivated vaccine that was developed and produced locally. It was prepared from the P3 strain of the JE virus (*3*) and approximately 70 million doses were administered annually (*4*). In 1988 a live attenuated vaccine (SA 14-14-2), also developed and produced locally, was licensed for use in China after studies had demonstrated its

[1] Epidemiologist, School of Public Health, Fudan University, Shanghai, China.
[2] Research Scientist, International Vaccine Institute, Seoul, Republic of Korea.
[3] Director, International Vaccine Institute, Seoul, Republic of Korea.
[4] Associate Research Scientist, International Vaccine Institute, Seoul, Republic of Korea.
[5] Senior Research Scientist, International Vaccine Institute, PO.Box 14, Shillim-Dong, Kwanak-Gu, Seoul 151-600, Republic of Korea (email: xuzhiyi@ivi.int). Correspondence should be addressed to this author.
Ref. No. **02-0451**.

safety and a high degree of efficacy (*1*). This vaccine has been routinely used in provinces of south-west China, more than 20 million doses being given annually (*4*).

Because these Chinese vaccines can be produced inexpensively, they are potentially attractive tools for other developing countries in Asia where JE is endemic. However, no studies on their cost-effectiveness have been reported. In order to obtain information on this matter we calculated the cost-effectiveness of a JE immunization programme in Shanghai, China, where the use of JE vaccines over many years provides an empirical basis for evaluating the economic consequences of vaccination.

Methods

Overview

We compared the costs and outcomes for three hypothetical cohorts of 100 000 neonates followed up to the age of 30 years which received the following: no JE vaccine; inactivated vaccine (P3); or live attenuated vaccine (SA 14-14-2). The setting for the analysis was Shanghai, where JE is endemic and JE immunization has been implemented since 1968 (Fig. 1). The purpose of following up to 30 years of age is to capture the disability associated with JE. Although most cases occur in young children in settings where the disease is endemic, the neurological sequelae can be frequent and permanent. Because we express costs in 1997 US$, the analysis models a birth cohort assembled in 1997 and followed up for 30 years after that date. The risk for JE in the cohort that does not receive JE vaccine is taken as the cumulative JE incidence rate from birth until 30 years of age, estimated from data reported during the prevaccination era in Shanghai between 1952 and 1967.

Construction of decision tree

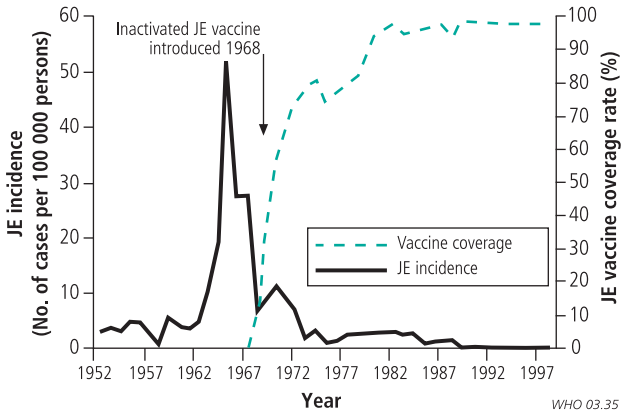
In order to compare the three strategies, a decision-analytical model was constructed (DATA, Version 3.5, TreeAge Software, Inc., Boston, MA, USA). The model considered all costs and outcomes related to JE in the hypothetical cohorts from birth until 30 years of age. The routine JE vaccination schedule in Shanghai was used in the model. The P3 vaccine was given in a five-dose schedule administered as two doses one week apart at 12 months of age and one dose at 2, 6, and 10 years of age. The SA 14-14-2 vaccine was administered in two doses, one at 12 months and the second at 2 years of age. A simplified decision tree for the analysis is presented in Fig. 2.

As in routine public health practice, children in the two cohorts targeted for vaccination could either receive or not receive vaccine, and, among those vaccinated, either complete or incomplete regimens could be administered. Vaccinated children could experience or not experience side-effects, which could either be mild or severe. Finally, the children could either develop or not develop JE, and, if they developed the disease, could survive without disability, survive with disability, or die during acute encephalitic illness.

Estimates of probabilities of health events

Data on the incidence of JE in Shanghai were abstracted from the infectious disease reporting system of the Centre for Disease Prevention and Control, Shanghai. The official statistics on JE in Shanghai for 1952–67 were reviewed in order to determine the average annual age-specific incidences for the disease before the JE immunization era (*5*). Before

Fig. 1. **Incidence of Japanese encephalitis (JE) and vaccine coverage of 1-year-olds with a two-dose primary series of P3 strain JE vaccine, Shanghai, China, 1952–98**



1967, epidemics of JE occurred approximately once every 15 years (*6*). There was one such epidemic between 1952 and 1967. Using the age-specific rates, we modelled the cumulative JE incidence for the period between birth and 30 years of age. We took this to represent the occurrence of JE in the non-vaccinated cohort and among non-vaccinated children in the cohorts targeted for vaccination (Fig. 1 and Fig. 3) (*7*), since the ecological determinants of the incidence of JE, such as meteorological conditions, the area of rice fields, the size of pig populations, the population density of mosquitos, and the level of seroprevalence of JE antibody in unvaccinated people and pigs were similar in the prevaccination and post-vaccination eras (*8*). Rates of inward and outward migration were assumed to be negligible in the three hypothetical cohorts.

On this basis we assumed an annual incidence of 35.2 cases per 100 000 persons under 10 years and a plausible range of annual incidences of 18.2–68.9 cases per 100 000 persons in the age group in question. These rates were comparable with rates observed in non-vaccinated control groups in previous JE vaccine trials in other provinces of China (*1*, *3*, *9*).

In order to estimate the vaccine coverage of children in Shanghai, we used reported coverage rates of the two-dose primary series of P3 vaccine in children aged 1 year between 1984 and 1998 (Fig. 1). Dose-specific coverage levels were not available for booster doses of P3 vaccine. In Shanghai, compliance with JE vaccination was very high and SA 14-14-2 vaccine had not been used previously. Our base-case analysis therefore assumed a 98% coverage level for all doses of the P3 and the SA 14-14-2 vaccines. However, in the sensitivity analysis we considered the effects of a lower level of coverage as well as the attrition of coverage associated with the last three doses of P3 vaccine (Table 1).

In order to estimate the dose-specific vaccine efficacy of both the P3 and SA 14-14-2 vaccines, we used published data describing neutralizing antibody responses following JE immunization, in conjunction with estimates of vaccine efficacy given in the literature on field trials conducted in China (Table 1). Studies of the inactivated vaccine showed that neutralizing antibody seroconversion rates were 60% after two doses, 93% after the third dose, and 100% after the fourth dose (*1*, *3*). The mean efficacy of the inactivated vaccine for a two-dose vaccine series in pre-licensing field trials was 85% (range

Fig. 2. **Simplified decision tree for the analysis of the cost-effectiveness of using either the P3 or the SA 14-14-2 strain of Japanese encephalitis (JE) vaccine in hypothetical cohorts of 100 000 neonates followed to 30 years of age in Shanghai, China.** Squares represent decision nodes and circles represent chance nodes. The branch for the immunization programme can refer either to that using P3 strain or SA 14-14-2 strain vaccine. Although vaccine adverse events are denoted as present or absent, the analysis considered mild and severe events separately. Similarly, although children are depicted as vaccinated or not vaccinated, the analysis considered each dose of the vaccine regimens separately

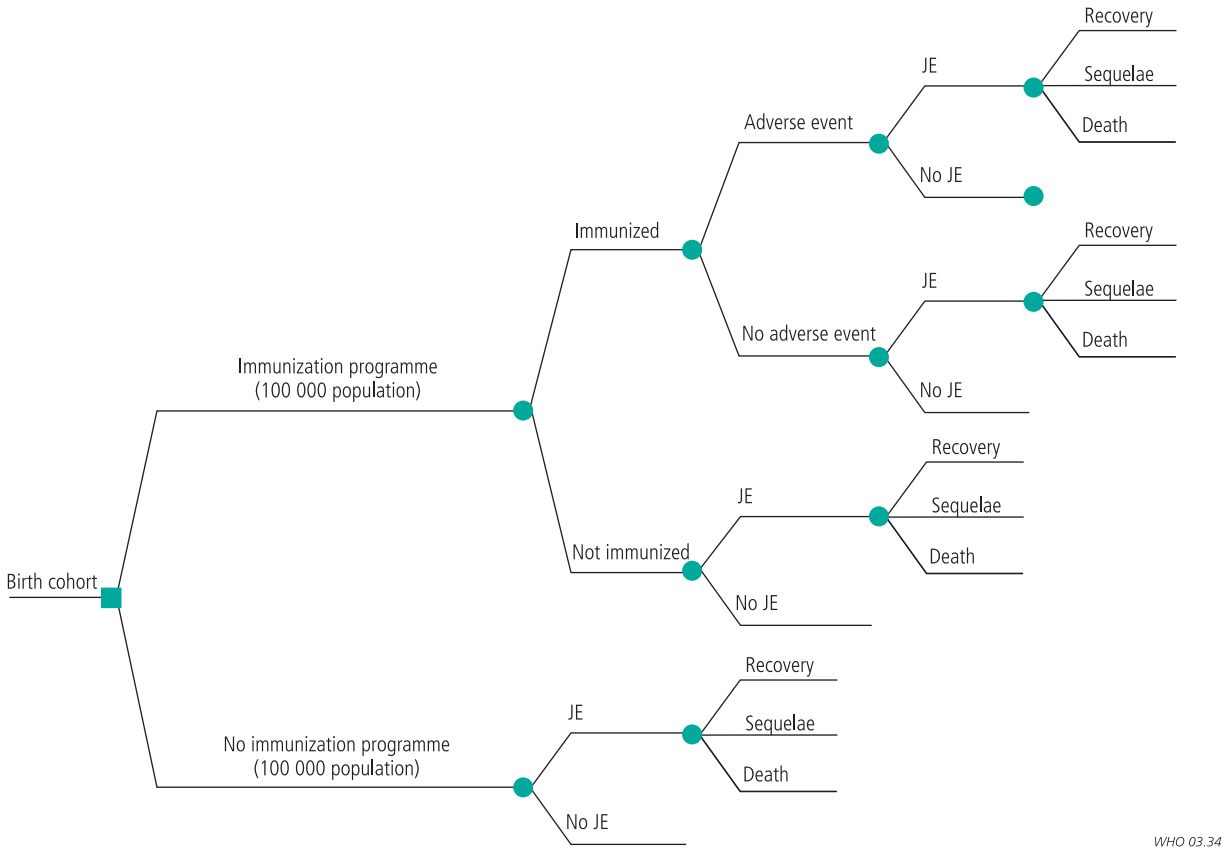
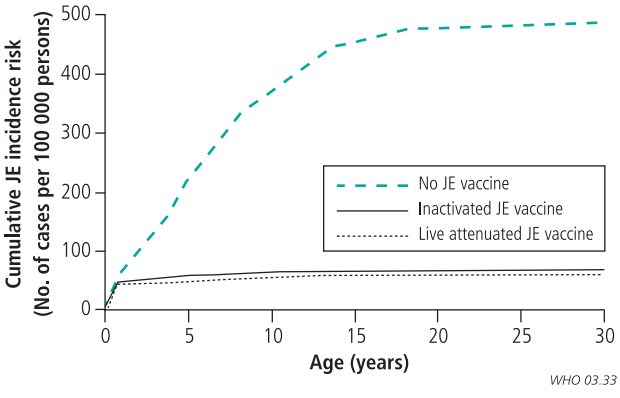


Fig. 3. **Cumulative risks of Japanese encephalitis (JE) from birth to 30 years of age for three immunization programme options: no JE vaccine, inactivated P3 strain JE vaccine, and live attenuated JE strain vaccine.** Risks are discounted as described in the text



76–95%) (*1*, *3*). No data are available on the efficacy of a single dose of the P3 inactivated vaccine. Because the protective efficacy of a single dose of inactivated mouse brain JE vaccine was reported as 50% *(9)*, it was assumed that this applied to a single dose of P3 vaccine. No data were available for the dose-specific efficacy after three, four, and five doses of P3 vaccine. Because the protective efficacy of the vaccine has been observed to be higher than neutralizing antibody seroconversion rates (*1*, *3*, *10*, *12*), we assumed that the efficacy of the inactivated vaccine was 50%, 85%, 95%, 98%, and 98% following the first, second, third, fourth and fifth doses, respectively. Field trials of the SA 14-14-2 vaccine showed protective efficacy levels ranging from 95% to 100% after receipt of a single dose (*1*, *3*, *10–12*, *33*), and vaccine efficacy after a second dose was reported as 98% (*13*). In our analysis we assumed that the vaccine conferred 95% protection after the first dose and 98% protection after the second dose. We also assumed that efficacy was sustained until the time of the next dose, and that, after the final dose, efficacy was maintained up to the age of 30 years (Fig. 3).

We considered both non-severe (e.g. local reactions and mild systemic reactions requiring only routine outpatient care) and severe reactions (e.g. systemic reactions requiring immediate or inpatient medical care) following the P3 vaccine. Vaccine-associated adverse events following each of the two doses of the SA 14-14-2 were all non-severe (Table 1) (*1*, *12–19*).

On the basis of previous studies (*1*, *2*, *20–23*) it was assumed that 25% of acute JE cases were fatal and that 30% of survivors had significant permanent neurological disability requiring chronic care (*5*, *20–28*). It was also assumed that the probabilities of death and disability following JE were the same

Table 1. **Parameter values and plausible ranges for variables used in the base-case and sensitivity analyses of Japanese encephalitis (JE) immunization programme options, Shanghai, China**

Variable	Base-case estimate	Plausible range	References
JE annual incidence (No. of cases per 10^5 under-10-year-olds)	35.2	18.2–68.9	*1, 3, 8*
Vaccine coverage per scheduled dose (%)	98	80–100	Unpublished data[a]
JE vaccine efficacy (%)			
P3 vaccine			*1, 3, 9*
Dose 1	50	50	
Dose 2	85	73–95	
Dose 3	95	92–99	
Doses 4 and 5	98	95–99	
SA 14-14-2 vaccine			*1, 10–13*
Dose 1	95	90–99	
Dose 2	98	94–99	
Vaccine-associated adverse events (events per dose per 10^4 persons)[b]			
P3 vaccine			
Non-severe reactions[c]	1.4	0.5–2.3	*15–19*
Severe reactions[c]	0.5	0.005–1.1	*15–19*
Non-severe reactions after SA 14-14-2 vaccine[d]	0.5	0.2–1.0	*1, 12–14*
JE case-fatality rate (%)	25	10–40	*5, 20–28*
% of JE cases with disability[e]	30	20–50	*19, 24–28*
Disability-adjustment weight[f] (by age group)			
0–14 years	0.616	–	*29*
15–30 years	0.613	–	*29*

[a] Personal communication, Bing Shen, Division of Epidemiology, Centre of Disease Prevention and Control, Jing An District, Shanghai, China, 1998.
[b] P3 vaccine administered in five-dose schedule and SA 14-14-2 vaccine administered in two-dose schedule.
[c] Non-severe and severe reactions are defined in the text.
[d] Adverse events of SA 14-14-2 vaccine are all non-severe reactions.
[e] Disability is defined as permanent neurological sequelae resulting in a need for chronic care.
[f] See text for details.

for both immunized and unimmunized children and that they were age-independent.

Disability-adjusted life years (DALYs) lost because of JE were calculated as the sum of years of life lost (YLLs) because of JE deaths and years lost as a consequence of living with disability (YLDs) associated with the neurological sequelae of JE (*29*). YLLs were calculated using age-specific life expectancies obtained from WHO life tables for China from birth to 30 years of age (*30*), together with the assumed values for the age-specific incidence of JE and the case-fatality rate of acute JE illness. We assumed that life expectancy to the age of 30 years was not shortened by post-JE disability. This assumption may have underestimated the DALYs lost because of JE, as some patients with disability died before the age of 30 years. YLDs were calculated by using published disability weights for JE and the assumed values for the age-specific incidence of JE and for the proportion of JE survivors experiencing significant disability (*29*).

Estimates for the numbers of JE cases, JE deaths and DALYs lost because of JE were discounted to their net present value in relation to the time of birth at the conventional annual rate of 3% (*31*).

Estimates of costs

Only direct costs (1997 US$) were used for this analysis and all costs were discounted to their net present values in relation to the time of birth at an annual rate of 3% (*31*). The costs associated with the vaccines, i.e. those of the vaccines and of items such as vaccine storage, salaries, transportation and supplies related to the conduct of the immunization programmes, were estimated from the charges for vaccination abstracted from actual costs incurred in China's Expanded Programme on Immunization (EPI), which are calculated to reflect total cost recovery (Table 2).

Costs related to the treatment of acute JE are those incurred for hospital inpatient care of the acute illness, for outpatient care of neurological sequelae, and for outpatient or inpatient care of vaccine-related adverse events.

In order to determine the cost of treatment for JE, charges were included for hospital beds, drugs, medical examinations, laboratory tests and medical personnel, which were calculated from data for JE patients treated in the Shanghai Medical School Children's Hospital. The outpatient treatment costs for JE-associated disability were estimated by senior neurologists, who interviewed the families of JE patients and reviewed the charges for the care of patients seen at the Shanghai Medical School Hua Shan Hospital. All of these reviews of medical care charges were conducted in the period 1990–97. There was no trend of change in the charges observed during this period and the mean costs were therefore calculated for the aggregate of data for the period without adjustment for inflation. Treatment costs for JE vaccine-associated adverse events were estimated by EPI staff of the Centre for Disease Prevention and Control of Jing An District, Shanghai.

Table 2. **Parameter values and plausible ranges for cost-related variables used in the base-case and sensitivity analyses of Japanese encephalitis (JE) immunization programme options, Shanghai, China**

Variable	Base-case estimate	Plausible range	References
Cost per dose of P3 or SA 14-14-2 vaccine (US$)	0.60	0.36–1.21	Unpublished data[a]
Cost per case of adverse events following vaccination (US$)			
Non-severe reaction[b]	3.60	1.20–6	Unpublished data[a]
Severe reaction[b]	18	6–30	Unpublished data[a]
Cost per case for acute care of JE illness (US$)		Unpublished data[c]	
Inpatient care (bed, nursing, treatment)	302	151–604	
Drugs	302	151–605	
Laboratory tests	242	121–484	
Medical examinations	363	182–725	
Total	1209	605–2418	
Cost per case per year for long-term care for disability following JE (US$)			Unpublished data[b]
Outpatient visit charge	6	–	
Drugs	30	4–33	
Laboratory tests	24	8–30	
Medical examinations	36	25–82	
Physiotherapy	25	5–30	
Total	121	48–181	
Annual discount rate for outcomes and costs	0.03	0–0.05	*29, 31*

[a] Personal communication, Bing Shen, Division of Epidemiology, Centre of Disease Prevention and Control, Jing An District, Shanghai, China, 1998.
[b] Personal communication, Zhen Hong, Department of Neurology, Hua Shan Hospital, Shanghai Medical University, 1998.
[c] Personal communication, Qi Rong Zhu, Department of Medical Records, Children's Hospital, Shanghai Medical University, 1998.

Measurement of cost-effectiveness

The total discounted JE cases, JE-associated deaths, and DALYs for each immunization strategy as compared with no immunization were calculated for the interval from birth to 30 years of age (*31*). The net cost savings of each immunization programme were estimated by subtracting the total costs of each from those that would have occurred in a programme involving no immunization. The cost-effectiveness ratio was calculated by dividing the net cost savings by the number of JE cases avoided (*31*). The influence of uncertainty about assumed values for each cost and outcome variable on the cost-effectiveness of JE immunization was evaluated by means of one-way sensitivity analyses that considered the extremes of the plausible range of values for each variable (Table 1 and Table 2).

Results

Base-case analysis of vaccine cost-effectiveness

In a cohort of 100 000 unvaccinated children who were followed up from birth to 30 years of age, the model predicted 488 cases and 122 deaths associated with JE (Table 3). In the absence of JE immunization it was estimated that the treatment of acute JE would cost US$ 483 672 and that 7441 DALYs would be lost because of JE, almost half attributable to post-JE neurological disability. Relative to the no-vaccination strategy, the use of P3 vaccine would result in 420 fewer JE cases, 105 fewer deaths and 6456 fewer DALYs lost. The corresponding values for the SA 14-14-2 vaccine would be 427 fewer JE cases, 107 fewer deaths, and 6556 fewer DALYs lost.

We estimated that the total direct costs associated with the treatment of JE and sequelae during the 30-year follow-up of 100 000 neonates who were not vaccinated would be US$ 738 315, and that the corresponding costs of using the P3 and SA 14-14-2 vaccines would be US$ 390 069 and US$ 225 859, respectively. The savings per 100 000 neonates would thus be US$ 348 246 and US$ 512 456, respectively. Consequently, the use of the SA 14-14-2 vaccine would be expected to result in a 47% greater financial saving than that associated with the use of the P3 vaccine. For each JE case prevented the use of the P3 and SA 14-14-2 vaccines would additionally save US$ 829 and US$ 1200, respectively (Table 3).

Sensitivity analyses

Table 4 shows the results of one-way sensitivity analyses for the variables whose ranges of uncertainty had the greatest impact on estimates of comparative costs for the vaccination strategies versus the no-vaccination strategy. The conclusions that both vaccination strategies would be cost saving and that the SA 14-14-2 vaccine strategy would be more cost saving than the P3 vaccine strategy remained intact in each of these analyses.

The JE incidence threshold above which vaccination would be cost saving would be 15.2 and 6.1 cases per 100 000 persons per year among under-10-year-olds for immunization programmes involving the use of the P3 and SA 14-14-2 vaccines, respectively. The use of these vaccines would be cost saving up to a vaccine cost of US$ 1.38 and US$ 3.30 per dose, respectively. The current cost of each vaccine is under US$ 1.00 per dose.

Discussion

Our results suggest that routine immunization with either the inactivated P3 vaccine or the live attenuated SA 14-14-2 vaccine would be cost saving for the health care system in Shanghai. However, the use of the SA 14-14-2 vaccine would yield a saving in costs 47% greater than that obtainable by using the P3 vaccine. Before considering the implications of this finding, we discuss the limitations of our analysis.

Table 3. **Summary of health outcomes and costs in the base-case analysis for three Japanese encephalitis (JE) immunization programme options, Shanghai, China**

	JE immunization programme option		
	No JE vaccine	Inactivated P3 vaccine	Live attenuated SA 14-14-2 vaccine
Outcomes (events per 10^5 persons)[a]			
No. of JE cases	488	68	61
No. of fatalities	122	17	15
No. of YLLs[b]	4279	567	510
No. of YLDs[c]	3162	417	375
Total DALYs[d]	7441	984	885
Outcomes prevented by immunization programme (events/10^5 persons)			
No. of JE cases	–	420	427
No. of fatalities	–	105	107
No. of DALYs[d]	–	6456	6556
Costs (US$ per 10^5 persons)[a]			
Immunization programme	–	265 894	114 175
Treatment of JE vaccine-associated adverse events	–	622	34
Treatment of acute JE illness	483 672	77 441	69 920
Treatment of disability following JE illness	254 643	46 112	41 730
Total costs (US$)	738 315	390 069	225 859
Net cost savings for treatment of acute JE illness (versus no vaccination)	–	406 231	413 752
Net cost savings for treatment of disability following JE illness (versus no vaccination)	–	208 531	212 913
Overall net cost savings of vaccination (versus no vaccination)	–	348 246	512 456
Net cost savings per prevented JE case	–	829	1200

[a] Outcomes and costs discounted annually at 3%. Costs are in 1997 US$.
[b] Years of life lost.
[c] Years lived with disability.
[d] Disability-adjusted life years.

Potential limitations

Our analysis did not consider the loss of patients' or families' wages associated with JE vaccination or with the care of people with JE and its long-term sequelae, and should therefore be considered as reflecting only the net costs to the health care system. It is difficult to predict how a consideration of indirect costs would have affected our findings, since the indirect costs associated with vaccination, a common event, would be expected to be minimal for each vaccinated child, whereas those associated with the prevention of JE, a rare event, would be expected to be quite large for each prevented case.

Our analysis was restricted to the first 30 years of life. However, the use of a vaccination strategy would have been favoured even more strongly had account been taken of the costs for treating JE disability and of the years of life lost because of JE disability, both of which continue to accrue after the age of 30 years.

We also assumed that there was no waning of immunity after each dose of JE vaccine. There are no published data that would guide estimates of vaccine-induced immunity over time for either of the vaccines under analysis. In areas where JE is endemic, however, even in the presence of waning vaccine-induced immunity, the natural boosting of immunity through exposure to wild-type JE virus during periods of intense transmission would probably maintain immunity at a high level.

Our model was based on data from institutions in Shanghai and our analysis considered only the two vaccines used and produced in China. Consequently, caution should be exercised in generalizing our findings to other settings and other JE vaccines.

Relationship to other studies on the cost-effectiveness of JE vaccines

In the only previous study that evaluated the cost-effectiveness of JE immunization in a setting where the disease was endemic, an inactivated vaccine derived from mouse brain was given to Thai children aged between 18 months and 6 years (*32*). The use of this vaccine was cost saving during the year after immunization. Clearly, such a short timeframe for analysis would not allow account to be taken of the benefits resulting from long-term vaccine effectiveness and the prevention of the delayed costs and morbidity from JE neurological sequelae. Our analysis, covering a 30-year period, presented a fuller assessment of the cost-effectiveness of vaccination, albeit with vaccines other than the one used in the Thai study.

Importance of considering disability in economic analyses of JE vaccines

We estimated the DALYs prevented by each of the JE immunization programmes. DALYs provide a parameter for comparing different health interventions within and between different health care systems and populations (*29*, *31*). The analysis of DALYs has some limitations, as illustrated by the somewhat arbitrary single published disability weights assigned to cover the diverse array of post-JE neurological sequelae (*29*). Notwithstanding these caveats, our analysis suggests that vaccination against JE with the P3 and SA 14-14-2 vaccines could prevent 87% and 88%, respectively, of the total disease burden of JE from birth to 30 years of age in Shanghai, as reflected by DALYs (Table 3). Moreover, considering the ratio

Table 4. **Sensitivity analyses comparing the cost savings associated with two strategies for Japanese encephalitis (JE) immunization**

Variable	Net cost savings associated with immunization strategy (US$ per 10^5 persons)[a]	
	Inactivated P3 vaccine	Live attenuated SA 14-14-2 vaccine
Base-case estimate	348 246	512 456
JE incidence (No. of cases per 10^5 under-10-year-olds)		
Lower limit: 18.2	51 396	209 890
Upper limit: 68.9	10 457 327	10 822 439
% of JE cases with disability		
Lower limit: 20%	278 736	441 485
Upper limit: 50%	487 267	654 397
Vaccine efficacy		
Lower limit: 90% — dose 1, 94% — dose 2 (SA 14-14-2 vaccine); 50% — dose 1, 73% — dose 2, 92% — dose 3, 95% — doses 4 and 5 (P3 vaccine)	325 791	486 404
Upper limit: 99% — dose 1, 99% — dose 2 (SA 14-14-2 vaccine); 50% — dose 2, 95% — dose 2, 99% — dose 3, 99% — doses 4 and 5 (P3 vaccine)	365 855	519 945
Vaccine coverage		
Lower limit: 80% — doses 1 and 2 (SA 14-14-2 vaccine); 80% — doses 1 and 2, 75% — doses 3, 4 and 5 (P3 vaccine)	292 750	418 187
Upper limit: 100% — doses 1 and 2 (SA14-14-2 vaccine); 100% — doses 1 and 2, 95% — doses 3, 4 and 5 (P3 vaccine)	363 983	522 930
Vaccine cost per dose		
Lower limit: 0.36	454 603	558 126
Upper limit: 1.21	77 921	396 378
Treatment cost for acute JE illness per case		
Lower limit: 605	145 299	305 751
Upper limit: 2418	754 477	926 208
Treatment cost of long-term sequelae following JE (per case per year)		
Lower limit: 48	222 438	384 004
Upper limit: 181	451 650	618 032
Annual discount rate for outcomes and costs		
Lower limit: 0 %	564 474	756 520
Upper limit: 5 %	256 128	405 877

[a] 1997 US$, discounted annually at 3% (see text).

of YLDs lost to DALYs lost because of JE in this model, 43% of the JE disease burden prevented by the JE vaccines is attributable to the prevention of long-term sequelae of JE disease (Table 3). About one-third of the cost savings attributable to vaccination would result from the prevention of chronic neurological sequelae. These findings underscore the importance of preventing disease sequelae as opposed to JE mortality per se in evaluating the benefits of vaccination against JE.

Implications for public health programmes

Our findings suggest that the use of the P3 vaccine in Shanghai was cost saving to the health care system and that similarly high levels of JE control might be achieved using the SA 14-14-2 vaccine with even greater cost savings.

Neither of the vaccines assessed in this analysis is licensed for use outside China. However, a recent demonstration project of the SA 14-14-2 vaccine in Nepal showed that it conferred a high degree of protection, even after a single dose (*33*). Moreover, it is reassuring that the inactivated JE vaccine derived from mouse brain, which is internationally licensed, proved cost saving in Thailand (*32*). It is thus likely that the economic benefits of vaccinating against JE are not limited to China or the Chinese vaccines.

Nonetheless, the introduction of JE vaccines for routine use in other countries where the disease is endemic can be expected to depend on several factors, including estimates of the disease burden, the availability of resources for vaccine purchase, the acceptability of JE vaccines and vaccine-associated adverse events, the perceptions of policy-makers concerning the need for and cost-effectiveness of JE vaccines, and competing public health priorities (*34*). Economic analyses can be powerful tools for informing policies on the rational introduction of JE vaccines into public health programmes. Special attention should be given to such analyses and to the improvement of surveillance systems in the many developing countries of Asia where JE is an important but neglected problem. ■

Acknowledgements

The project was supported financially by the Bill and Melinda Gates Children's Vaccine Program, Program for Appropriate Technology in Health, Seattle, WA, USA. (contract number 00-GAT.770-790-01149-LPS).

We thank Dr Qi-Rong Zhu, Children's Hospital, Shanghai Medical School; Dr Zhen Hong, Institute of Neurology, Hua Shan Hospital, Shanghai Medical School; and Dr Bing Shen, Centre of Disease Prevention and Control, Jing An District, Shanghai for technical assistance.

Conflicts of interest: none declared.

Résumé

Coût-efficacité de la vaccination systématique dans la lutte contre l'encéphalite japonaise à Shanghai (Chine)

Objectif Evaluer le rapport coût-efficacité des vaccins inactivés et des vaccins vivants atténués contre l'encéphalite japonaise administrés aux nourrissons et aux enfants à Shanghai.

Méthodes Un modèle d'analyse de décision a été élaboré en vue de comparer les coûts et les issues pour trois cohortes hypothétiques de 100 000 enfants suivis depuis leur naissance en 1997 jusqu'à l'âge de 30 ans et ayant reçu soit aucun vaccin contre l'encéphalite japonaise, soit un vaccin inactivé (P3), soit un vaccin vivant atténué (SA-14-14-2). Les valeurs de l'incidence cumulée des cas d'encéphalite japonaise de la naissance à l'âge de 30 ans à une époque où il n'y avait pas de vaccination contre cette maladie, c'est-à-dire avant 1968, ont été utilisées pour estimer les taux d'encéphalite japonaise qui seraient attendus en l'absence de vaccination. Les conséquences économiques ont été mesurées en termes de coût par cas, par décès et par année de vie ajustée sur l'incapacité (DALY) que chacun des deux programmes de vaccination contre l'encéphalite japonaise aurait permis d'éviter.

Résultats Par rapport à l'absence de vaccination, un programme utilisant le vaccin P3 éviterait 420 cas et 105 décès et économiserait 6456 DALY pour 100 000 personnes ; l'utilisation du vaccin SA 14-14-2 éviterait 427 cas et 107 décès et économiserait 6556 DALY pour 100 000 personnes. Les deux programmes de vaccination permettraient de réaliser des économies mais la stratégie utilisant le vaccin SA 14-14-2 entraînerait une économie supérieure de 47 % (US $512 456) par rapport à l'utilisation du vaccin P3 (US $348 246).

Conclusion Les deux stratégies de vaccination contre l'encéphalite japonaise permettraient de réaliser des économies par rapport à l'absence de vaccination. Il s'agit là d'un solide argument en faveur de la vaccination contre cette maladie à Shanghai et qui permet en outre de penser que la vaccination contre l'encéphalite japonaise pourrait se justifier sur le plan économique dans d'autres parties de la Chine et dans certains autres pays en développement d'Asie où cette maladie est endémique.

Resumen

Relación costo-eficacia de la inmunización sistemática contra la encefalitis japonesa en Shanghai (China)

Objetivo Evaluar la relación costo-eficacia de las vacunas inactivada y viva atenuada contra la encefalitis japonesa (EJ) administradas a lactantes y niños en Shanghai.

Métodos Se construyó un modelo analítico de decisiones para comparar los costos y los resultados en tres cohortes hipotéticas de 100 000 niños seguidos desde su nacimiento en 1997 hasta la edad de 30 años, los cuales o bien no recibieron vacuna anti-EJ, o bien recibieron la vacuna anti-EJ inactivada (P3), o bien recibieron la vacuna anti-EJ viva atenuada (SA 14-14-2). Se emplearon las incidencias acumuladas de EJ entre el nacimiento y los 30 años en los años preinmunización, es decir, antes de 1968, para estimar las tasas esperadas de EJ en ausencia de vacunación. Las consecuencias económicas se cuantificaron determinando el costo por caso, por defunción y por AVAD (año de vida ajustado en función de la discapacidad) evitado en los dos programas de inmunización contra la EJ.

Resultados En comparación con la ausencia de vacunación contra la EJ, un programa basado en la vacuna P3 prevendría 420 casos de EJ y 105 defunciones por EJ y permitiría un ahorro de 6456 AVAD por 100 000 personas; usando la vacuna SA 14-14-2 se prevendrían 427 casos y 107 muertes y se ahorrarían 6556 AVAD por 100 000 personas. Ambos tipos de inmunización permitían ahorrar costos, pero la estrategia basada en la vacuna 14-14-2 permitió un ahorro superior en un 47% (US$ 512 456) al obtenido con la vacuna P3 (US$ 348 246).

Conclusión Las dos estrategias de inmunización contra la EJ redundaron en ahorros de costos en comparación con la falta de inmunización contra la enfermedad. Esto constituye un argumento económico de peso para vacunar contra la EJ en Shanghai, y lleva a pensar que la vacunación contra la EJ podría estar justificada desde el punto de vista económico en otras partes de China y en otros países en desarrollo de Asia donde la enfermedad es endémica.

ملخص

مردودية التمنيع الروتيني في مكافحة التهاب الدماغ الياباني في شنغهاي، الصين

الغرض: تقييم مردودية اللقاحات المعطَّلة واللقاحات الحية الموهَّنة لالتهاب الدماغ الياباني التي تعطى للرضع وللأطفال في شنغهاي.

الطريقة: تم إنشاء نموذج للتحليل ولاتخاذ القرار لكي نقارن التكاليف والنتائج لدى ثلاث مجموعات افتراضية من الأتراب لمئة ألف طفل تمت متابعتهم منذ ولادتهم عام ١٩٩٧ حتى بلوغهم سن الثلاثين، كما لو تلقَّت مجموعة منهم ثلاث جرعات من اللقاح المعطّل لالتهاب الدماغ الياباني وتلقت المجموعة الثانية اللقاح الحي الموهَّن لالتهاب الدماغ الياباني SA 14-14-2) فيما لم تتلقَّ المجموعة الثالثة أي لقاح، وقد استخدمت معدلات الحدوث التراكمية لالتهاب الدماغ الياباني منذ الولادة وحتى سن الثلاثين قبل عهد التمنيع؛ أي قبل عام ١٩٦٨، لتقديم المعدلات المتوقعة من التهاب الدماغ الياباني في غياب التمنيع ضده. وقد قيست العواقب الاقتصادية وفق التكلفة لكل حالة على حدة، ولكل حالة وفاة، وكل سنة ضائعة من سنوات العمر المصححة باحتساب مدد العجز، وذلك بالنسبة للبرنامجين اللذين تم فيهما التمنيع ضد التهاب الدماغ الياباني.

الموجودات: عند المقارنة بالمجموعة التي لم تتلق أي تمنيع ضد التهاب الدماغ الياباني فإن البرنامج الذي يفترض أنه استخدم فيه التمنيع بثلاث جرعات من اللقاح كان سيقي من وقوع ٤٢٠ حالة من حالات التهاب الدماغ الياباني ومن موت ١٠٥ حالات أخرى وسيستنقذ ٦٤٥٦ سنة من سنوات العمر المصححة باحتساب مدد العجز لدى كل مئة ألف من الناس؛ أما البرنامج الذي استخدم فيه التمنيع بلقاح SA 14-14-2 فكان سيقي من وقوع ٤٢٤ حالة من حالات التهاب الدماغ الياباني ومن موت ١٠٧ حالة أخرى وسيستنقذ ٦٥٥٦ سنة من سنوات العمر المصححة باحتساب مدد العجز لدى كل مئة ألف من الناس، وكلا نمطي التمنيع كان سيؤدي إلى توفير في التكاليف، إلا أن الاستراتيجية التي تعتمد على استخدام اللقاح SA 14-14-2 كانت ستؤدي إلى توفير مقداره ٥١٢ ٤٥٦ دولاراً أمريكياً وهو أكبر ٤١٪ مما كانت ستؤدي إليه الاستراتيجية التي تعتمد على التلقيح بثلاث جرعات من اللقاح المعطل والتي كانت ستؤدي إلى توفير مقداره ٣٤٨ ٢٤٦ دولاراً أمريكياً.

الاستنتاج: إن كلا الاستراتيجيتين اللتين تعتمدان على استخدام التمنيع ضد التهاب الدماغ الياباني يؤدي إلى توفير في التكاليف إذا ما قورنتا بعدم التمنيع ضده. وفي ذلك تبرير اقتصادي قوي للتمنيع ضد التهاب الدماغ الياباني في شنغهاي، مما يشير أيضاً إلى أن التطعيم ضد التهاب الدماغ الياباني قد يكون مبرراً أيضاً للاستخدام في أجزاء أخرى من الصين وفي البلدان الآسيوية النامية الأخرى التي يتوطن فيها هذا المرض.

References

1. Tsai TF, Chang GJ, Yu YX. Japanese encephalitis vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. Philadelphia (PA): WB Saunders; 1999. p. 672-703.
2. Pieper SJL, Kurland LT. Sequelae of Japanese B and mumps encephalitis. *The American Journal of Tropical Medicine and Hygiene* 1958;7:481-98.
3. Gu PW, Ding ZF. Inactivated Japanese encephalitis (JE) vaccine made from hamster cell culture (a review). *JE and HFRS Bull* 1987;2:15-26.
4. Yu YX. Japanese encephalitis in China. *Southeast Asian Journal of Tropical Medicine and Public Health* 1995;26 Suppl. 3:17-21.
5. [*The epidemiological analysis of Japanese encephalitis in Shanghai, 1952–1979*]. Shanghai: Centre of Disease Prevention and Control; 1980. In Chinese.
6. Ding D, Xu ZY. [Retrospective analysis of incidence of Japanese encephalitis in Shanghai]. *Chinese Journal of Vaccine and Immunology* 2001;7:147-9. In Chinese.
7. Kahn HA, Sempos CT. Follow-up studies: life tables. In: Kahn HA, Sempos CT, editors. *Statistical methods in epidemiology*. New York: Oxford University Press; 1989. p. 168-205.
8. Shen B, Ding D, Li YT, Lu JD, Zhao LL, Hu JY, et al. [Study on ecological factors for secular changes in incidence of Japanese encephalitis in Shanghai]. *China Public Health* 2002;18:308-9. In Chinese.
9. Hsu TC, Chow LP, Wei HY, Chen LL, Hsu ST, Huang CT, et al. A completed field trial for an evaluation of the effectiveness of mouse-brain Japanese vaccine. In: McD Hammon W, Kitaoka M, Downs WG, editors. *Immunization for Japanese encephalitis*. Amsterdam: Excerpta Medica; 1972. p. 285-91.
10. Wang JL, Na JC, Zhao SS, Wang J, Zhang KZ, Wang WL, et al. [An epidemiological study of the efficacy of live Japanese encephalitis vaccine]. *Chinese Journal of Biology* 1993;36-7. In Chinese.
11. National Serum and Biologics Institute, Jiling Yang Gi Health Station. [Studies on immunization schedules for Japanese encephalitis vaccine]. *Chinese Journal of Preventive Medicine* 1984;6:360-3. In Chinese.
12. Ma WX, Yu YX, Wang SG, Zhou BL, Ma YH, Feng SY, et al. [Safety and efficacy of live-attenuated Japanese encephalitis vaccine]. *Chinese Journal of Biology* 1993;6:245-8. In Chinese.
13. Hennessy S, Liu ZL, Tsai TF, Strom BL, Wan CM, Liu HL, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA-14-14-2): a case–control study. *Lancet* 1996;347:1583-6.
14. Huang ZL, Li XG, Wu JN, Deng HF. [Side-effects of live-attenuated Japanese encephalitis vaccine]. *Chinese Journal of Zoonosis* 1998;14:60-1. In Chinese.
15. Jiangsu Anti-Epidemic Centre. [Adverse events after the immunization of Japanese encephalitis vaccine in Jiangsu, 1993–1997]. In: *Annual report of Neimenggu Anti-Epidemic Centre 1998*. In Chinese.
16. Shanghai Anti-Epidemic Centre. [The side-effects of Japanese encephalitis vaccine in Shanghai, 1995–1997]. In: *Report of Shanghai Anti-Epidemic Centre 1998*. In Chinese.
17. Xie GZ. [The immunization and prevention of Japanese encephalitis]. *Chinese Journal of Vaccines and Immunization* 1996;2:85-7. In Chinese.
18. Ma FB, Sun XD, Ying Y, Ding XZ, Xu WZ, Yu LG, et al. [Prospective studies on the immunization reactions of inactivated Japanese B encephalitis (JBE) vaccine]. *Chinese Journal of Vaccines and Immunization* 2000;6:203-5. In Chinese.
19. Xie GZ. [Japanese encephalitis. In: Zha WY, editor. *Expanded Programme on Immunization*]. Shanghai: Shanghai Medical and Technical Publishing Company; 1997. p. 402-9. In Chinese.
20. Huang ZX, Song G, Tian FD. [Epidemiological survey of Japanese encephalitis in Beijing, 1948–1950]. *Chinese Journal of Medicine* 1951;37:253-76. In Chinese.
21. Jiang Z, Zhu FT. [Clinical report of 414 child patients with Japanese encephalitis in Beijing]. *Chinese Journal of Paediatrics* 1952;141-54. In Chinese.
22. Jin FL, Tian BX, Wu B. [Causes of death in Japanese encephalitis]. *Chinese Journal of Internal Medicine* 1955;7:530-5. In Chinese.
23. Fan PL, Hu SY. [Japanese encephalitis epidemic in Chengdu]. *Chinese Journal of Medicine* 1951;37:308-16. In Chinese.
24. Zhong HL, Yan JQ, Zhu FT. [Diagnosis, outcome and treatment of Japanese encephalitis]. *Chinese Journal of Medicine* 1953;11:815-33. In Chinese.
25. Yu JG. [Factors affecting outcome of Japanese encephalitis in children]. *Chinese Journal of Clinical Paediatrics* 1992;10:152-3. In Chinese.
26. Tao WY. [Analysis of 50 Japanese encephalitis patients]. *Journal of Nanjing Medical University* 1993;13:84. In Chinese.
27. Huang XY, Yuan WZ. [Clinical characteristics of Japanese encephalitis in children in Quanzhou]. *Jiangxi Medicine* 1995;30:254. In Chinese.
28. Luo D, Song J, Ying H, Yao R, Wang Z. Prognostic factors of early sequelae and fatal outcome of Japanese encephalitis. *Southeast Asian Journal of Tropical Medicine and Public Health* 1995;26:694-8.
29. Murray CJL, Lopez AD. *The global burden of disease*. Boston (MA): Harvard School of Public Health on behalf of the World Health Organization and The World Bank; 1996 (Global Burden of Disease and Injury Series Vol. 1).
30. Lopez AD, Salomon J., Ahmad O, Murray CJL, Mafat D. *Life tables for 191 countries: data, methods and results*. Geneva: World Health Organization; 2001. Global Programme on Evidence for Health Policy Discussion Paper No. 9. Available from: URL: http://whqlibdoc.who.int/hq/2001/a78629.pdf
31. Haddix AC, Teutsch SM, Shaffer PA, Dunet DO. *Prevention effectiveness: a guide to decision analysis and economic evaluation*. New York: Oxford University Press; 1996.
32. Siraprapasiri T, Sawaddiwudhipong W, Rojanasuphot S. Cost-benefit analysis of Japanese encephalitis vaccination program in Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* 1997;28:143-8.
33. Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case-control study. *Lancet* 2001;358:791-5.
34. Liu Y, Hsiao WC, Eggleston K. Equity in health and health care: the Chinese experience. *Social Science and Medicine* 1999;49:1349-56.