Immunogenicity and safety of measles-rubella vaccine co-administered with attenuated Japanese encephalitis SA 14–14–2 vaccine in infants aged 8 months in China: a non-inferiority randomised controlled trial

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See Comment page 344

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or

Summary

Background In China, measles-rubella vaccine and live attenuated SA 14–14–2 Japanese encephalitis vaccine (LJEV) are recommended for simultaneous administration at 8 months of age, which is the youngest recommended age for these vaccines worldwide. We aimed to assess the effect of the co-administration of these vaccines at 8 months of age on the immunogenicity of measles-rubella vaccine.

Methods We did a multicentre, open-label, non-inferiority, two-group randomised controlled trial in eight counties or districts in China. We recruited healthy infants aged 8 months who had received all scheduled vaccinations according to the national immunisation recommendations and who lived in the county of the study site. Enrolled infants were randomly assigned (1:1) to receive either measles-rubella vaccine and LJEV simultaneously (measles-rubella plus LJEV group) or measles-rubella vaccine alone (measles-rubella group). The primary outcome was the proportion of infants with IgG antibody seroconversion for measles 6 weeks after vaccination, and a secondary outcome was the proportion of infants with IgG antibody seroconversion for rubella 6 weeks after vaccination. Analyses included all infants who completed the study. We used a 5% margin to establish non-inferiority. This trial was registered at ClinicalTrials.gov (NCT02643433).

Findings 1173 infants were assessed for eligibility between Aug 13, 2015, and June 10, 2016. Of 1093 (93%) enrolled infants, 545 were randomly assigned to the measles-rubella plus LJEV group and 548 to the measles-rubella group. Of the infants assigned to each group, 507 in the measles-rubella plus LJEV group and 506 in the measles-rubella group completed the study. Before vaccination, six (1%) of 507 infants in the measles-rubella plus LJEV group and one (<1%) of 506 in the measles-rubella group were seropositive for measles; eight (2%) infants in the measles-rubella plus LJEV group and two (<1%) in the measles-rubella group were seropositive for rubella. 6 weeks after vaccination, measles seroconversion in the measles-rubella plus LJEV group (496 [98%] of 507) was non-inferior to that in the measles-rubella group (499 [99%] of 506; difference –0·8% [90% CI –2·6 to 1·1]) and rubella seroconversion in the measles-rubella plus LJEV group (478 [94%] of 507) was non-inferior to that in the measles-rubella group (473 [94%] of 506 infants; difference 0·8% [90% CI –1·8 to 3·4]). There were no serious adverse events in either group and no evidence of a difference between the two groups in the prevalence of any local adverse event (redness, rashes, and pain) or systemic adverse event (fever, allergy, respiratory infections, diarrhoea, and vomiting). Fever was the most common adverse event (97 [19%] of 507 infants in the measles-rubella plus LJEV group; 108 [21%] of 506 infants in the measles-rubella group).

Interpretation The evidence of similar seroconversion and safety with co-administered LJEV and measles-rubella vaccines supports the co-administration of these vaccines to infants aged 8 months. These results will be important for measles and rubella elimination and the expansion of Japanese encephalitis vaccination in countries where it is endemic.

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Introduction

Measles is a highly contagious disease that requires high population immunity (93–95%) for elimination. Vaccinating all eligible children with two doses of measles vaccine is the standard for national immunisation programmes aimed at eliminating measles, with on-time delivery of the first dose of measles-containing vaccine (MCV) being the highest priority.[1] Rubella is an infectious disease with similar—although milder—symptoms to measles. Rubella virus is highly teratogenic, especially

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Research in context

Evidence before this study

Administration of live, attenuated SA 14–14–2 Japanese encephalitis vaccine (LJEV) has been introduced or is being considered by many countries, but evidence is scarce on the immunogenicity and safety of measles-rubella vaccine when the two vaccines are co-administered in routine infant immunisation. In China, measles-rubella vaccine and LJEV are recommended for simultaneous administration at 8 months of age, which is the earliest recommended age globally. We did a literature review of studies published from database inception to June 30, 2018, in PubMed and two large scientific online Chinese databases (Wanfang and CNKI) using the search terms "measles vaccine", "Japanese encephalitis", and "immunogenicity". We found only one trial that demonstrated no interference of LJEV on single-antigen measles vaccine among infants at 9 months of age but no trials that assessed the impact of LJEV on immunogenicity of measles-rubella vaccine in infants were identified.

Added value of this study

This study found that infants aged 8 months seroconverted equally well to measles and rubella whether measles-rubella vaccine was administered alone or simultaneously with LJEV. To our knowledge, this is the first study assessing the immunogenicity of measles-rubella when co-administered with LJEV. Our data also showed that before measles-rubella vaccination, infants aged 8 months had low measles and rubella titres, whereas after measles-rubella vaccination, these infants showed high proportions of seroconversion and seropositivity for measles and rubella.

Implications of all the available evidence

Given the high proportion of seroconversion needed for protective immunity to measles and the increasing number of countries that have started administering rubella-containing vaccines—usually as measles-rubella—in childhood immunisation schedules, our findings are important for measles elimination, rubella control, and expansion of Japanese encephalitis vaccination in endemic countries.

during the first trimester of pregnancy, when it causes congenital rubella syndrome, a constellation of severe birth defects of the eyes, ears, heart, and brain.[2] In 2005, the second dose of measles vaccine was moved to 18–24 months of age. In 2008, rubella vaccination was included in China's National Immunisation Programme, with a schedule of measles-rubella vaccine given at 8 months of age and measles-mumps-rubella vaccine given at 18 months of age.

Japanese encephalitis is the most important vaccine-preventable cause of encephalitis in many Asian countries, with an estimated 68 000 clinical cases every year, primarily among children.[3,4] Approximately 50% of these cases occur in mainland China. Vaccination is considered essential for Japanese encephalitis control in endemic areas,[5] and WHO recommends integration of Japanese encephalitis vaccine into national immunisation schedules in all areas where Japanese encephalitis is recognised as a public health priority.[6] A live, attenuated, SA 14–14–2 Japanese encephalitis vaccine (LJEV) is manufactured in China and has been prequalified by WHO since October, 2013. This vaccine has been used in China and other Asian countries, such as Nepal, South Korea, Sri Lanka, India, Thailand, Cambodia, Vietnam, and Laos.[7,8] China's National Immunisation Programme has included LJEV since 2008, with one dose given at 8 months and a second dose given at 2 years of age. In China, LJEV and measles-rubella vaccine are recommended for co-administration at 8 months, which is the earliest administration age of these vaccines across the countries using Japanese encephalitis vaccine. Available evidence supports the immunogenicity and safety of co-administration of LJEV with single-antigen measles vaccine among infants, but there are no studies of co-administration of LJEV and measles-rubella vaccine at 8 months of age.[6] Furthermore, WHO's position on measles vaccine is that MCV administered before 9 months of age should be considered supplementary (ie, should not count as one of the two routine MCV doses) unless the country has data showing high seroconversion after vaccination of infants younger than 9 months.[9]

In this Article, we report a study to evaluate seroconversion and possible LJEV interference with measles-rubella vaccination when co-administered at 8 months of age.

Methods

Study design

We did a multicentre, open-label, non-inferiority randomised controlled trial in eight counties or districts in two provinces in China; three counties were in the Hebei province (Wangdu, Dingxing, and Gaobeidian in the Baoding prefecture) and five counties or districts were in the Zhejiang province (Fenghua and Yinzhou in the Ningbo prefecture, and Songyang, Jinyun, and Qingtian in the Lishui prefecture). We compared seroconversion when measles-rubella vaccine and LJEV are co-administered with seroconversion when measles-rubella vaccine is given without LJEV. We also assessed the safety and tolerance for co-administered LJEV and measles-rubella vaccine. This study was approved by the ethical review committee of the China Center for Disease Control and Prevention (CDC; approval number, 201518);

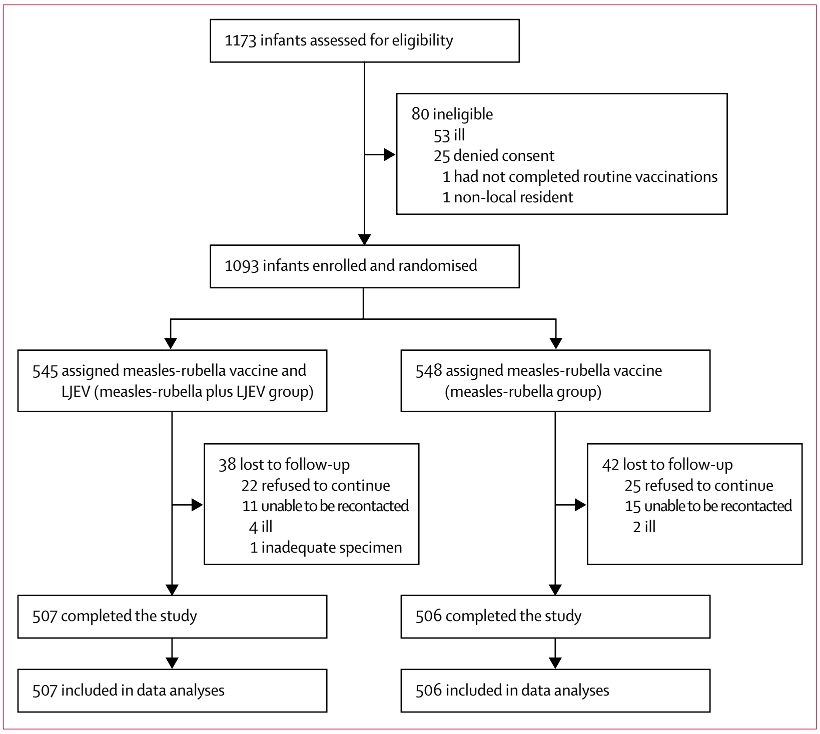

Figure 1: **Trial profile**
LJEV=live, attenuated SA 14–14–2 Japanese encephalitis vaccine.

US CDC was designated as a non-engaged collaborator for institutional review board purposes.

Participants

Eligible participants were infants aged from 8 months to 8 months and 2 weeks, who had received all scheduled vaccinations according to the national immunisation recommendations, who lived in the county of the study site, whose parents or legal guardians stated willingness to participate for the entire study period, and who had no contraindications to vaccination. Exclusion criteria were a history of measles, rubella, or Japanese encephalitis; previous receipt of measles, rubella, or Japanese encephalitis vaccines; receipt of blood products or immunosuppressive therapy within the previous 3 months; and receipt of any live vaccines within the previous 4 weeks or of any inactivated vaccines within the previous 2 weeks.

Parents or legal guardians of participating infants gave their written informed consent before study enrolment and allocation to a study group.

Randomisation and masking

The sample size was apportioned equally to the two provinces (Hebei and Zhejiang) by setting each province's target sample size to one half of the total target sample size. Infants were enrolled and randomly assigned to be administered either measles-rubella vaccine and LJEV simultaneously (measles-rubella plus LJEV group) or measles-rubella vaccine alone (measles-rubella group). To achieve a balance of study-group assignment among clinics, infants in the same clinic were randomly assigned to one of the two groups using a 1:1 block randomisation scheme with a block size of eight (four per group). Randomisation lists were completed before enrolment by the China CDC and given to participating clinics. Grouping information of each participant was concealed in a separate envelope, and only after enrolment was grouping information revealed to the field investigators and to the infants' parents or legal guardians. Investigators and participants' parents were not masked to study group assignment to avoid the need to give a placebo injection to the infants in the measles-rubella group. Laboratory staff analysing sera were masked to assignment; investigators analysing data and assessing outcomes were not masked to assignment.

Procedures

After enrolment, infants received vaccines (measles-rubella vaccine and LJEV or measles-rubella vaccine only) according to their group assignment. Infants in the measles-rubella plus LJEV group received two injections at different injection sites during the same visit; infants in the measles-rubella group received a single injection. 6 weeks after enrolment, infants in the measles-rubella group were given LJEV. At the initial visit, following enrolment, study staff used a uniform questionnaire to collect basic information about the participants, including: date of birth, sex, gestational age, birthweight, status of breast feeding, mother's age, history of measles, rubella, or Japanese encephalitis, and information about maternal vaccination.

Vaccines used in this study were single-dose domestically produced vaccines, lot-released by the China Food and Drug Administration. The measles-rubella vaccine used in this study was produced by Beijing Tiantan Biological Products Company (Beijing, China) and was composed of the Shanghai 191 strain of measles virus, a widely used strain in China since the 1960s, and the BRD-II strain of rubella virus vaccine, which has been used in China since the 1980s. The SA 14–14–2 Japanese encephalitis vaccine we used was produced by Chengdu Biological Products Institute (Chengdu, China). It was licensed in the 1980s, has been recommended for universal use in China's National Immunisation Programme since 2008, and was prequalified by WHO in 2013.

We collected two blood samples from each infant. The first sample was obtained before vaccination to measure baseline measles and rubella antibody concentrations, and the second sample was obtained 6 weeks (42–48 days) after vaccination to assess measles and rubella antibody responses to vaccination.

Measles and rubella IgG antibody concentrations were determined using an ELISA kit produced by Virion\Serion (Wurzburg, Germany). Measles seropositivity was defined as a measles IgG antibody concentration greater than 200 mIU/mL; rubella IgG antibody titres greater than 10 IU/mL were considered seropositive. Sero conversion for antibodies against each virus was defined as a change from seronegative to seropositive or a four-times or more increase in IgG antibody concentration between samples collected at baseline and 6 weeks after vaccination. We consider rubella and measles sero-positivity to be protective concentrations of antibodies.[10–13] Seroconversion for Japanese encephalitis virus was not assessed.

Outcomes

The primary outcome was non-inferiority of sero-conversion for measles in the measles-rubella plus LJEV group versus the measles-rubella group. Co-administration of measles-rubella vaccine and LJEV was considered non-inferior to measles-rubella vaccine alone if the lower confidence interval was above the inferiority margin of –5%. The primary outcome was assessed by a single laboratory in Zhejiang province. Secondary outcomes were non-inferiority of seroconversion for rubella in the measles-rubella plus LJEV group versus the measles-rubella group and adverse events in the 6 weeks after vaccination. We also did a post-hoc analysis of measles and rubella IgG antibody concentrations. Primary, secondary, and additional outcomes were assessed among infants completing the study, in a per-protocol analysis.

We actively monitored adverse events following immunisation (AEFIs) based on the WHO Global Manual on Surveillance of AEFIs.[14] Participating infants were observed for immediate AEFI for 30 min after vaccination. A diary card was given to parents or guardians to record observed local or systemic reactions for 6 weeks. Parents or guardians of participating infants were prompted to look for local reactions of redness, swelling, induration, rash, and pain; and systemic reactions of fever, allergy, vomiting, diarrhoea, cough, running nose, and crying. Parents or guardians were asked to report any other possible reactions, and to report medications and other vaccinations received. Parents or guardians were contacted by telephone on the 7th day, 14th day, and 28th day after vaccination to check on their record-keeping, to follow up on reported AEFIs, and to answer any questions. At the 6-week visit, the diary cards were reviewed with the parent or guardian to ensure completion and address any questions about the recordings. Each AEFI was classified as mild, moderate, severe, or very severe according to the guidelines for adverse event classification standards for vaccine clinical trials, released by the China Food and Drug Administration in 2005 (appendix).

Statistical analysis

We assumed a 93% proportion of seroconversion against measles after administration of measles-rubella vaccine alone. A sample size of 447 individuals per group was required for a power of 0·90 with a one-sided α of 0·05 and a non-inferiority margin of –5% with a Z test with pooled variance. We used a 5% margin of non-inferiority rather than a 10% margin because measles eradication requires high population immunity, and high measles seroconversion is, therefore, necessary for a measles immunisation strategy. Assuming 15% loss to follow-up, we aimed to recruit 526 infants per group.

The data collection system used in this study was based on the electronic data collection platform of the China CDC. Data were entered online and were able to

	Measles-rubella plus LJEV group (n=507)	Measles-rubella group (n=506)
Height, median (IQR), cm	71·0 (69·0–73·0)	71·0 (69·0–73·0)
Weight at enrolment, median (IQR), kg	9·0 (8·4–10·0)	9·0 (8·2–9·8)
Weight at birth, mean (SD), kg	3·32 (0·42)	3·31 (0·43)
Mother's age, median (IQR), years	27·6 (24·6–31·0)	27·1 (24·5–30·3)
Sex		
Male	263 (52%)	278 (55%)
Female	244 (48%)	228 (45)
Low birthweight		
Yes	14 (3%)	13 (3%)
No	493 (97%)	493 (97%)
Premature		
Yes	13 (3%)	17 (3%)
No	494 (97%)	489 (97%)
Birth history		
Eutocia	262 (52%)	261 (52%)
Caesarean	245 (48%)	245 (48%)
Feeding pattern		
Breastfeeding	371 (73%)	364 (72%)
Weaning	83 (16%)	107 (21%)
Never breastfed	53 (10%)	35 (7%)
History of maternal measles		
Yes	42 (8%)	40 (8%)
No	385 (76%)	375 (74%)
Unknown	80 (16%)	91 (18%)
History of maternal rubella		
Yes	1 (<1%)	4 (1%)
No	416 (82%)	408 (81%)
Unknown	90 (18%)	94 (19%)
Maternal measles vaccination		
Yes	49 (10%)	44 (9%)
No	82 (16%)	74 (15%)
Unknown	376 (74%)	388 (77%)
Maternal rubella vaccination		
Yes	6 (1%)	8 (2%)
No	131 (26%)	116 (23%)
Unknown	370 (73%)	382 (75%)

Data are n (%) unless otherwise indicated. LJEV=live, attenuated SA 14–14–2 Japanese encephalitis vaccine.

Table 1: **Characteristics of infants and their mothers**

For the **China Food and Drug Administration guidelines for adverse event classification standards for vaccine clinical trials** see http://www.sda.gov.cn/WS01/CL1616/83435.html

See **Online** for appendix

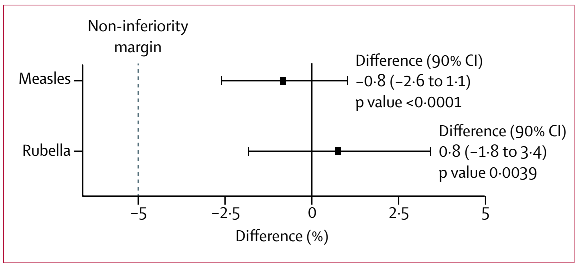

Figure 2: **Seroconversion for measles and for rubella in the measles-rubella plus LJEV group versus the measles-rubella group**
Non-inferiority was assessed by calculating the difference in proportion of seroconversion for measles and for rubella between the measles-rubella plus LJEV group and the measles-rubella group and a two-sided 90% CI (Farrington-Manning). We defined a non-inferiority margin of –5%. LJEV=live, attenuated SA 14–14–2 Japanese encephalitis vaccine.

	Measles-rubella plus LJEV group (n=507)	Measles-rubella group (n=506)	p value
Measles			
Seropositive prevalence before vaccination	6 (1·2%, 0·5)	1 (0·2%, 0·2)	0·12*
Seropositive prevalence after vaccination	501 (99%, 0·5)	500 (99%, 0·5)	1·0†
Seroconversion proportion	496 (98%, 0·6)	499 (99%, 0·5)	<0·0001‡
Rubella			
Seropositive prevalence before vaccination	8 (2%, 0·5)	2 (0·4%, 0·3)	0·11*
Seropositive prevalence after vaccination	483 (95%, 0·9)	475 (94%, 1·1)	0·33†
Seroconversion proportion	478 (94%, 1·0)	473 (93%, 1·1)	0·0039‡

Data are n (%, SE). *Fisher's Exact test. †Pearson χ^2 test. ‡Non-inferiority p value (Farrington-Manning) test, α=0·05.

Table 2: **Measles and rubella IgG antibody seropositivity and seroconversion before and after vaccination**

	Measles-rubella plus LJEV group (N=507)	Measles-rubella group (n=506)	p value
Measles			
Pre-vaccination concentration (mIU/mL)	25 (25–25)	25 (25–25)	0·25
Post-vaccination concentration (mIU/mL)	1830·9 (1319·5–2419·9)	1739·7 (1294·4–2259·9)	0·06
Rubella			
Pre-vaccination concentration (IU/mL)	2·7 (2·1–3·7)	2·7 (2·2–3·5)	0·82
Post-vaccination concentration (IU/mL)	56·4 (34·3–85·0)	58·9 (32·3–88·5)	0·63

Data are median (IQR); Z value and p value were calculated with non-parametric Wilcoxon rank-sum tests. The Virion test kit lower limit of detection for measles antibody was 50 mIU/mL, and values below 50 mIU/mL were assigned to 25 mIU/mL.

Table 3: **Measles and rubella IgG antibody concentrations before and after vaccination**

be immediately reviewed and examined for data quality control by China CDC investigators. After final data cleaning, personal identifying information was removed to create an analytic database.

We compared distributions (medians and IQRs) using rank sum testing for non-normal, continuous variables (ie, height, weight at enrolment, mother's age, measles and rubella IgG antibody concentration). We compared normally distributed, continuous variables (ie, weight at birth) using Student's *t* tests (means with 95% CI). For categorical variables (ie, sex, low birthweight, premature, birth history, history of maternal measles, history of maternal rubella, maternal measles vaccination, maternal rubella vaccination, seropositive, seroconversion), we compared frequencies and proportions using Pearson's χ^2 test or Fisher's exact test. For non-inferiority tests, we calculated a two-sided, 90% CI (Farrington-Manning) of the difference between the measles-rubella plus LJEV group and the measles-rubella group. All data analyses were done with SAS 9.4.

This study is registered with ClinicalTrials.gov, number NCT02643433, and it is completed.

Role of the funding source

The funder of the study participated in study design, data analysis, data interpretation, and writing of the report, but not in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1173 infants were assessed for eligibility between Aug 13, 2015, and June 10, 2016, and 80 were excluded (figure 1). Of 1093 infants enrolled, 545 were randomly assigned to the measles-rubella plus LJEV group and 548 to the measles-rubella group. 1013 (93%) enrolled infants completed the study, 507 in the measles-rubella plus LJEV group and 506 in the measles-rubella group (figure 1); 504 infants were from the Hebei province and 509 from the Zhejiang province. Characteristics of the participants and their mothers are shown in table 1. There was little difference between the two groups in infant weight at enrolment or in maternal characteristics (age, and measles and rubella disease and vaccination history; appendix).

Before vaccination, six (1%) of 507 infants in the measles-rubella plus LJEV group and one (<1%) of 506 in the measles-rubella group were seropositive for measles; eight (2%) infants in the measles-rubella plus LJEV group and two (<1%) in the measles-rubella group were seropositive for rubella antibody. 6 weeks after vaccination, seropositivity for measles antibody increased to 99% in both groups (501 of 507 infants in the measles-rubella plus LJEV group; 500 of 506 infants in the measles-rubella group; p=0·9973), yielding a non-inferior proportion of seroconversion of 98% in the measles-rubella plus LJEV group (496 of 507 infants) and of 99% in the measles-rubella group (499 of 506 infants; difference –0·8% [90% CI –2·6 to 1·1], $p_{non\text{-}inferiority}$<0·0001; figure 2 and table 2). 6 weeks after vaccination, 483 (95%) of 507 infants in the measles-rubella plus LJEV group and 475 (94%) of 506 infants in the measles-rubella group were seropositivie for the rubella antibody (p=0·33), yielding a non-inferior proportion of seroconversion of 94·3% in the measles-rubella plus LJEV group (478 of 507 infants) and of 93·5% in the measles-rubella group

(473 of 506 infants; difference 0·8% [90% CI –1·8 to 3·4], $p_{non\text{-}inferiority}$=0·0039; figure 2 and table 2).

The median concentration of measles IgG antibody was 25 mIU/mL in both groups before vaccination (the Virion test kit lower limit of detection for measles antibody was 50 mIU/mL, and values below 50 mIU/mL were assigned to 25 mIU/mL); after vaccination, the median concentration of measles IgG antibody increased to 1830·9 mIU/mL in the measles-rubella plus LJEV group and to 1739·7 mIU/mL in the measles-rubella group, with no significant difference between groups (table 3). The median concentration of rubella IgG antibody was 2·7 IU/mL in both groups before vaccination; after vaccination, it increased to 56·4 IU/mL in the measles-rubella plus LJEV group and 58·9 IU/mL in the measles-rubella group, with no significant difference between groups (p=0·63; table 3).

Among the seven infants who were seropositive for measles before the measles-rubella vaccination at 8 months of age, prevaccination IgG concentrations ranged from 411·4 mIU/mL to 1604·7 mIU/mL. Among these infants, only the infant with the lowest prevaccination IgG antibody concentration seroconverted, showing a four-time increase from 411·4 mIU/mL to 1810·2 mIU/mL. The other six did not seroconvert—ie, none had a four-time rise in measles IgG antibody titres (appendix).

Among the ten infants who were seropositive for rubella antibody before the measles-rubella vaccination at 8 months of age, prevaccination IgG concentrations ranged from 10·4 IU/mL to 357·6 IU/mL. Three of these infants seroconverted, with 5·0-times to 6·5-times increases in IgG antibody concentrations after vaccination. The other seven infants did not seroconvert after vaccination; one infant's IgG antibody concentration increased by 3·8-times, near the threshold for seroconversion. Four of the infants included in this study were seropositive for measles and rubella antibody before the measles-rubella vaccination; none of these four seroconverted to either vaccine component (appendix).

AEFI information was collected for all infants who completed the study. Mild local reactions included redness, swelling, and pain; systemic reactions included fever, diarrhoea, and vomiting. There were no serious AEFIs (table 4; appendix). In the measles-rubella plus LJEV group, seven (1%) of 507 infants were reported to have one or more local AEFI; in the measles-rubella group, 14 (3%) of 506 infants were reported to have one or more local AEFI. There was no evidence of a difference in the incidence of any local AEFI between the two groups (χ^2=2·40, p=0·12). Systemic AEFI were reported in the 6 weeks following vaccination for 144 (28%) infants in the measles-rubella plus LJEV group and 162 (32%) infants in the measles-rubella group. There was no evidence of a difference in the incidence of any systemic AEFI between the two groups (χ^2=1·57, p=0·21; table 4). Fever was the most common systemic AEFI. All infants with reported AEFIs fully recovered.

	Measles-rubella plus LJEV group (n=507)			Measles-rubella group (n=506)	p value*
	Combined n (%)†	Measles-rubella n (%)	LJEV n (%)		
Local adverse events					
Redness	11 (1%)	6 (1%)	5 (1%)	12 (2%)	0·15
Swelling	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	..
Induration	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	..
Pain	8 (1%)	4 (1%)	4 (1%)	2 (<1%)	0·69‡
Rash	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0·50‡
Any event	19 (2%)	7 (1%)	12 (2%)	14 (3%)	0·12
Systemic adverse events					
Fever	97 (19%)	..	..	108 (21%)	0·38
Allergy	9 (2%)	..	..	5 (1%)	0·28
Vomiting	6 (1%)	..	..	8 (2%)	0·59
Diarrhoea	15 (3%)	..	..	23 (5%)	0·18
Cough	24 (5%)	..	..	26 (5%)	0·77
Running nose	12 (2%)	..	..	14 (3%)	0·69
Crying	7 (1%)	..	..	10 (2%)	0·46
Upper respiratory infection	14 (3%)	..	..	9 (2%)	0·29
Others	16 (3%)	..	..	8 (2%)	0·10
Any event	144 (28%)	..	..	162 (32%)	0·21

Data are n (%); infants can have more than 1 reported event; p values were calculated with Pearson's χ^2 test, unless otherwise specified. *The p values for local reactions are for the comparison between the measles-rubella vaccine injection sites. †n=1014 (ie, two injection sites per patient). ‡Fisher's exact test.

Table 4: **Reported adverse events following immunisation (AEFIs)**

Discussion

In this study, we found that measles and rubella IgG antibody seroconversion following measles-rubella vaccination was not adversely affected by co-administration with LJEV at 8 months of age. The high rates of seroconversion and high antibody concentration against measles and rubella viruses found in both groups provide reassurance that infants will be protected from both measles and rubella, whether the first dose of measles-rubella is given alone or co-administered with LJEV. These data support the integration of LJEV into routine childhood immunisation schedules in countries where Japanese encephalitis vaccine is part of the national immunisation schedule or where Japanese encephalitis is endemic and introduction of the vaccine is being considered. Co-administration of the two vaccines might be particularly useful in areas with scarce resources or access to care, as it would avoid the extra costs and inconvenience associated with an additional clinic visit, possibly leading to greater uptake.

The safety profile for simultaneous administration of LJEV with measles-rubella vaccine was similar to that of measles-rubella vaccine alone. Both vaccines have been in use for decades in China and are considered safe. Passive postmarketing surveillance of Japanese encephalitis vaccination in China between 2008 and 2013 has found no safety concerns, with 214·4 AEFIs reported per million doses of administered LJEV.[15] During these years, 39·0% of the time Japanese encephalitis vaccine was co-administered with other vaccines—of which MCV was the most common (62·7%).[15] As expected, the active adverse-event monitoring we used in our study found a higher prevalence of AEFIs than were identified in passive, postmarketing surveillance.

Our results are consistent with a study done in Taiwan,[16] which showed co-administration of live attenuated Japanese chimeric virus vaccine with measles-mumps-rubella at 9 months did not affect measles and rubella antibody seroconversion proportions compared with a measles-mumps-rubella only group. Although Japanese chimeric virus vaccine is a different class of Japanese encephalitis vaccine than LJEV, the consistency of findings is reassuring.

LJEV co-administration and measles seroconversion were assessed in a randomised study[17] done in 2005–06 of infants aged 9 months in the Philippines. The investigators showed the proportion of measles seroprotection (defined as IgG antibody concentration ≥340 mIU/mL) in infants co-administered a single antigen measles vaccine and LJEV was not inferior to the proportion of seroprotection in infants receiving the measles vaccine and LJEV separately (95·5% [95% CI 91·9–97·8] *vs* 100% [98·0–100]). In addition, the proportion of Japanese encephalitis seroprotection in the group that was co-administered measles vaccine plus LJEV was non-inferior to that in the LJEV-alone group (90·5% [85·9–94·1] *vs* 92·1% [84·3–96·7]). The geometric mean concentration for measles antibody titres[18] in the measles vaccine and LJEV co-administration group (302 mIU/mL) was higher than in the measles vaccine-alone group (263 mIU/mL), and the proportion of measles seroprotection in the measles vaccine and LJEV co-administration group was non-inferior to the proportion in the measles vaccine-alone group (91·8% [87·3–95·1] *vs* 86·5 [80·6–91·2]). In our study, we used the same LJEV vaccine as in the study[17,18] done in the Philippines and our results provide additional assurance that LJEV does not have an adverse effect on the immune response to measles vaccine.

A non-randomised, single-group study[19] of 257 Sri Lankan infants who received simultaneous doses of LJEV and measles vaccine reinforced the safety profile of LJEV vaccine, but because there was no control group, the effect of LJEV on measles antibody seroconversion could not be measured.

LJEV has been introduced or is being considered by many countries for routine infant immunisation, but because high proportions of seroconversion are needed for protective population immunity to measles virus, immunogenicity and safety data on the possible effects of co-administering LJEV on the effectiveness of measles vaccine are crucial.[1] The non-inferiority and safety of co-administered LJEV and measles-rubella vaccine shown in this randomised trial support the concomitant delivery of these vaccines in infants—a finding of importance to the global priorities of measles eradication and of expansion of Japanese encephalitis vaccination in endemic countries.[8] This study also showed no reduction in rubella antibody seroconversion with concomitant administration of LJEV and measles-rubella vaccine. This information is particularly useful given the widespread introduction of rubella vaccination, with 152 countries having included rubella-containing vaccines (usually as measles-rubella vaccine) in their national childhood immunisation schedules as of December, 2016.[20]

An additional finding of specific relevance for China is that the infants aged 8 months in this study had low measles and rubella antibody titres before vaccination, whereas after measles-rubella vaccination, the prevalence of seropositivity to measles and rubella antibody was high (98%). This result countervails the concern that maternal antibodies interfere with the immune response to measles-rubella vaccine in infants younger than 9 months. WHO recommends the first dose of MCV to be administered at 9 months of age, and that MCV administered before this age should be considered a supplementary dose and not count as one of the two routine MCV doses unless the country has seroconversion data for MCV administered before age 9 months.[9]

Our study is consistent with previous observations that pre-existing measles and rubella antibody will prevent seroconversion, as only 14% and 30% of infants with pre-existing antibodies to measles and rubella, respectively, seroconverted. The numbers of infants in these categories were small, but only about 1% of infants aged 8 months in our study were seropositive before vaccination. This finding suggests that maternal measles antibody had waned by this age, providing further support for the administration of measles-rubella vaccine to infants aged 8 months in China.

A limitation is that comparison of results between different ELISA tests is problematic because of the different sources and concentrations of antigens, and thresholds for determining protective antibody concentrations have not been standardised.[10] Thus, it is difficult to make a direct comparison of antibody concentrations in our study with the concentrations measured in studies that used other ELISA kits. A second potential limitation is the loss to follow-up of 80 (7%) of 1093 enrolled infants who did not complete the study. However, proportion of participants lost to follow-up was similar in each group and most losses to follow-up were due to parents refusing to continue until the end of the 6 weeks of the study or being unreachable. Only six infants did not complete the study because of illness after enrolment. Because the proportion of loss to follow-up did not differ substantially between study groups, and among infants who completed the study, the two groups were not substantially different from each other in height, weight, sex, prevalence of low birthweight, and feeding pattern (appendix), we believe it is unlikely that losses to follow-up biased our seroconversion and safety results. Loss to follow-up was approximately half of the proportion accounted for in the sample-size calculation, indicating that study power was not compromised.

Overall, we found that infants aged 8 months seroconverted equally well to measles and rubella when measles-rubella vaccine was administered alone and simultaneously with LJEV. Proportions of seroconversion were high and consistent with the proportion necessary to eradicate measles and rubella. No safety concerns were identified for either of the vaccines used in this study, regardless of whether measles-rubella vaccine was co-administered with LJEV. Co-administration of these two vaccines can reduce the number of needed immunisation visits and the time and effort dedicated by health workers, parents, and caregivers. Measles-rubella and LJEV co-administration has, therefore, the potential of increasing the coverage of Japanese encephalitis, measles, and rubella vaccination and of protecting an increased number of young infants from the morbidity and mortality associated with these three serious diseases.

Contributors

YL, CY, HW, YW, LR, QX, ZF, and ZA conceptualised and designed the study; YL, HW, and ZA designed the data collection instruments; SX, FZ, YZ, RM, YL, ZZ did and supervised the field investigation and collected the data; YL, HW, and ZA carried out the initial analyses; SYC, KW confirmed the data analysis plan and data analysis results; and YL, SYC, KW, HW, and ZA drafted the initial manuscript. All authors revised the manuscript, approved the submitted version, and agree to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

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