Measles vaccine immunogenicity after coadministration with live attenuated Japanese encephalitis vaccine shows equivalence to that of measles vaccine given alone

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Background

Japanese encephalitis (JE) is the leading viral cause of disability in children in Asia with approximately 70 percent of patients either dying or suffering long-term neurological sequelae. One dose of live attenuated JE vaccine (LJEV) provides greater than 96 percent protection for up to 5 years, and single-dose immunization with LJEV, in routine immunization combined with campaigns among all at risk population, now provides simplified prevention strategies. However, concurrent administration of LJEV with measles vaccine (MV) in routine immunization programs had not been evaluated. Therefore, this study assessed the noninferiority of the immunogenicity of measles vaccine given with LJEV at 9 months of age compared to that of measles vaccine given alone, as well as the safety and tolerability of coadministration.

Methods

Healthy infants were randomized to receive either LJEV at 8 months of age and MV at 9 months [Group 1 (n=98)]; LJEV and MV coadministered at 9 months [Group 2 (n=235)]; or MV at 9 months and LJEV at 10 months [Group 3 (n=223)] (ITT). Prevaccination and one month postvaccination antibodies for measles and JE were tested by ELISA and PRNT, respectively. Noninferiority is achieved if the two-sided 95 percent confidence interval lower bound (CI LB) of the difference in measles seropositivity rates between Groups 2 and 3 is less than 10%.

Philippines Clinical Trial Design

Subjects aged from 9 to 11 months old were randomized into three Groups:

- Group 1: Received the first dose of JE vaccine alone and measles one month later.
- Group 2: Received simultaneously JE and measles vaccine.
- Group 3: Received measles vaccine alone and JE vaccine one month later as a benefit.

Titer Results

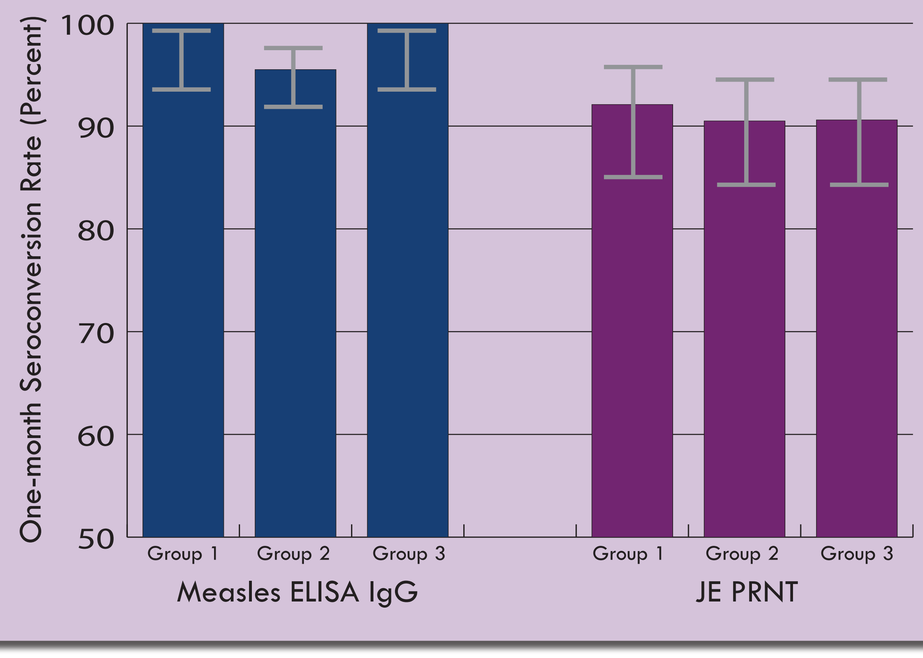
Titers (GMTs) obtained one month after the vaccination for measles and JE antibodies.

Test	Day	Group 1	Group 2	Group 3
Measles ELISA IgG	Day 0	223	228	225
	Day 28	3241	2471	3205
JE PRNT	Day 0	Not Detected	Not Detected	Not Detected
	Day 28	279	221	195

Results

Measles seroprotection rates (≥340 mIU/mL) at one month postvaccination were 100.0% (Group 1), 95.5% (Group 2), and 100.0% (Group 3) for a difference in measles seropositivity rates between Groups 2 and 3 of -4.5% (95% CI LB, -7.2%). The geometric mean titers for measles antibodies in Groups 1, 2, and 3 were 3241, 2471, and 3205, respectively. For JE antibodies, seroprotection rates (≥1:10) at one month postvaccination were 92.1% (Group 1), 90.5% (Group 2), and 90.6% (Group 3) for a difference in JE seropositivity rates between Groups 1 and 2 of -1.5% (95% CI LB, -8.3%). All vaccinations were well tolerated between the Groups.

Seroprotection Results (One-month Seropositivity Rates and Corresponding 95% CIs)



This table below shows the difference of seroprotection in percent and 95% CIs between groups. Our statistical hypothesis was that the lower bound of the 95% CIs of the difference of seroprotection rate observed between Group 2 and Group 3 was not more than 10% in order to demonstrate statistically the non inferiority of the measles immunity between Group 2 and Group 3. The difference between Group 2 and Group 3 observed was 4%.

Comparison of Group-specific Seroprotection Rates

All confidence interval lower bounds of the differences in seroprotection rates were higher than the noninferiority cutoff of -10%.

Test	Comparison	Difference in seroprotection rates (%) [95% CI]
Measles ELISA IgG	Measles vaccine coadministered with JE vaccine (Group 2) vs. Measles vaccine given alone (Group 3)	-4% [-6, -1] Noninferiority confirmed
JE PRNT	JE vaccine coadministered with measles vaccine (Group 2) vs. JE vaccine given alone (Group 1)	-1.5 [-8, 5] Noninferiority confirmed

Conclusions

The coadministration of LJEV and MV at 9 months of age showed anti-measles and anti-JE immunogenicity equivalent to LJEV and MV given separately. Safety profiles were comparable. These results remove scientific barriers for introducing LJEV into routine EPI schedules with MV, and will make the introduction of LJEV into routine EPI programs easier, without the need of an additional vaccination visit.