Immunogenicity and safety of combined measles-mumps-rubella-varicella vaccine using new measles and rubella working seeds in healthy children in Taiwan and Singapore
A phase II, randomized, double-blind trial

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Abbreviations: ATP, according-to-protocol; CCID_{50}, median cell culture infective dose (50%); CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean titer; IFA, immunofluorescence assay; mIU/mL, milli international unit per milliliter; MMR, measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine; MMRV_{new WS}, measles-mumps-rubella-varicella vaccine manufactured with measles and rubella monovalent bulks derived from a newly established working seed virus; SAE, serious adverse event; SAS®, Statistical Analysis System

Introduction

Measles, mumps, rubella and varicella are viral diseases associated with significant morbidity and mortality in children and sometimes linked with potentially life-threatening complications. Effective vaccination strategies coupled with sustained high vaccination coverage can reduce the risk of transmission of such highly infectious viruses. The success of a two-dose measles-mumps-rubella (MMR) vaccination strategy is evident in European countries where a significant reduction in disease morbidity and mortality has been noted. On the other hand, although varicella vaccines are licensed in many countries, they are not always included in national immunization programs and as a result the vaccine uptake is low. Nevertheless, evidence of the impact of universal varicella vaccine coverage (80%) has been observed in the United States and Uruguay.

The Taiwan national immunization program incorporated two-dose MMR and one-dose varicella vaccinations as separate injections in 1992 and 2004, respectively. Despite high coverage rates for the first-doses of MMR (96%) and varicella (97%) vaccinations, measles and varicella outbreaks and varicella breakthrough infections have occurred.

Aim: This study evaluated the immunogenicity and safety of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine produced with measles and rubella monovalent bulks derived from a newly established working seed virus stock (MMRV_{new WS}) compared with the combined MMRV vaccine derived from the current seed virus stock, in Taiwanese and Singaporean children (NCT00892775).

Results: Non-inferiority of MMRV_{new WS} to MMRV was achieved for all vaccine antigens. The lower limits of the 95% confidence intervals for group differences (MMRV_{new WS} group vs. MMRV) for measles (99.4% vs. 100%), mumps (89.7% vs. 90.4%), rubella (99.7% vs. 100%) and varicella (97.6% vs. 92.9%) seroconversion rates were greater than -10%. Mild symptoms including a peak in fever between days 5 and 12, post-dose-1, was observed in both groups.

Methods: Healthy children aged 11–22 mo were randomized to receive two doses of either the MMRV_{new WS} vaccine or the MMRV vaccine. Antibody titers against measles, mumps and rubella were measured using ELISA and against varicella using an immunofluorescence assay. The primary objective was to demonstrate non-inferiority of MMRV_{new WS} to MMRV in terms of post-dose-1 seroconversion rates, defined as a group difference with a lower limit of the 95% confidence interval greater than -10% for each antigen. Parents/guardians recorded symptoms in diary cards for 43 d after each vaccine dose.

Conclusion: The immune responses elicited by the MMRV_{new WS} vaccine were non-inferior to that elicited by the MMRV vaccine for all antigens. Both vaccines exhibited an acceptable safety profile in Taiwanese and Singaporean children.
Singapore, the introduction of two-dose MMR vaccination in 1999 resulted in a considerable decline in reported cases for all three diseases. While varicella vaccination has been available in Singapore since 1996, it is not included in the childhood vaccination schedule.\(^\text{15}\)

A combined MMR-varicella vaccine (MMRV) may achieve the higher vaccination coverage rates needed to achieve the full benefits of varicella vaccination and facilitate the inclusion of varicella into national immunization programs.\(^\text{16}\) Such a vaccine has the potential to provide broad protection against four diseases in a single injection and with minimum impact on vaccination program logistics.\(^\text{16}\) A tetravalent MMRV vaccine was developed based on previous experience with MMR and varicella vaccines.\(^\text{7}\) Previous studies have demonstrated that the MMRV vaccine is as immunogenic as separate MMR and varicella vaccines.\(^\text{17-19}\) The MMRV vaccine is commercially available in Australia, Canada and several European countries as a two-dose schedule.\(^\text{7,20}\)

Recently, production of GlaxoSmithKline’s combined MMRV vaccine was switched to measles and rubella monovalent bulks derived from a newly established working seed virus stock (MMRV\text{new WS}) due to the depletion of the current working seed virus stock. The new working seed virus stock is one passage further than the current working seed virus stock. This study was undertaken to obtain clinical data on the immunogenicity and safety of MMRV\text{new WS}, by assessing its non-inferiority to MMRV when administered to healthy Taiwanese and Singaporean children.

### Results

**Demographics.** Of 498 children enrolled in the study (332 in the MMRV\text{new WS} group; 166 in the MMRV group), 475 were
MMRV

new WS and MMRV groups in terms of seroconversion rates 43 d post-dose-1 was greater than the pre-specified cut-off (-10%) (Table 1).

Safety and reactogenicity. The overall incidence of symptoms (solicited and unsolicited) was 88.3% in the MMRV new WS and 85.5% in the MMRV groups following dose-1; and 68.5% in the MMRV new WS and 72.0% in the MMRV groups, following dose-2. Injection site redness was the most commonly reported solicited local and grade 3 symptom in both groups during the 4-d period after each dose (Table 2). Fever was the most commonly reported solicited general symptom in both groups during the 43-d period after each dose (Table 3). After dose-2, fever was reported for fewer children in both groups. A peak in the prevalence of fever between days 5 and 12 was observed post-dose-1 (Fig. 2).

In the MMRV new WS group, febrile convulsions occurring during the 43-d post-vaccination period were reported in two children (days 16 and 38 post-dose-1), accompanied by acute pharyngitis in the first child and viral infection in the second child. The second child experienced another febrile convolution

| Dose         | MMRV

new WS group | MMRV group | Difference in SC rate (MMRV

new WS - MMRV) | P-value |
|-------------|------------|-----------------|---------|
| N | SC (%) (95% CI) | GMT (95% CI) | N | SC (%) (95% CI) | GMT (95% CI) | Value (%) (95% CI) |
| Anti-measles (≥ 150 mIU/ml) – ELISA |
| Post-dose-1 | 314 | 99.4 (97.7; 99.9) | 3291.2 (3054.0; 3546.8) | 157 | 100 (97.7; 100) | 3460.1 (3145.6; 3806.0) | -0.64 (-2.29; 1.76) | < 0.0001 |
| Post-dose-2 | 308 | 100 (98.8; 100) | 4247.6 (3911.5; 4612.6) | 156 | 100 (97.7; 100) | 4297.1 (3867.9; 4774.0) | - | - |
| Anti-mumps (≥ 231 U/ml) – ELISA |
| Post-dose-1 | 311 | 89.7 (85.8; 92.9) | 924.4 (821.9; 1039.7) | 157 | 90.4 (84.7; 94.6) | 994.4 (851.7; 1161.0) | -0.74 (-6.14; 5.58) | 0.0004 |
| Post-dose-2 | 307 | 100 (98.8; 100) | 3379.5 (3121.3; 3659.0) | 155 | 100 (97.6; 100) | 3216.2 (2870.9; 3603.0) | - | - |
| Anti-rubella (≥ 4 IU/ml) – ELISA |
| Post-dose-1 | 314 | 99.7 (98.2; 100) | 71.7 (66.1; 77.9) | 157 | 100 (97.7; 100) | 66.6 (59.3; 74.9) | -0.32 (-1.78; 2.08) | < 0.0001 |
| Post-dose-2 | 308 | 100 (98.8; 100) | 125.7 (117.4; 134.5) | 156 | 100 (97.7; 100) | 115.2 (104.2; 127.4) | - | - |
| Anti-varicella (≥ 25 mIU/ml) – ELISA |
| Post-dose-1 | 291 | 97.6 (95.1; 99.0) | 104.8 (90.8; 120.9) | 141 | 92.9 (87.3; 96.5) | 69.6 (53.6; 90.2) | 4.69 (0.72; 10.34) | < 0.0001 |
| Post-dose-2 | 286 | 100 (98.7; 100) | 6570.6 (5746.7; 7512.7) | 138 | 100 (97.4; 100) | 5134.8 (4153.8; 6347.4) | - | - |

MMRV

new WS, measles-mumps-rubella-varicella vaccine derived from newly established working seed virus stock; MMRV: measles-mumps-rubella-varicella vaccine derived from current working seed virus stock; ELISA, Enzyme-linked immunosorbent assay; IFA: immunofluorescence assay; N, number of children with available results; SC: seroconversion; GMT: geometric mean titer; 95% CI: Exact 95% confidence interval; P-value, one-sided asymptotic standardized test for H0: MMRV

new WS – MMRV < -10%; Note: 30 children in the MMRV

new WS group and 16 children in the MMRV group received commercially available MMRV vaccine as the second dose due to expiry of initial vaccine lots and were included in the ATP cohort.
The results demonstrated that immune responses to measles, mumps, rubella and varicella post-dose-1 of MMRV new WS vaccine were non-inferior to that elicited by the MMRV vaccine. The primary non-inferiority criterion of ruling out a 10% difference in seroconversion rates post-dose-1 of MMRV new WS compared with MMRV was achieved for all antigens.

The observed seroconversion rates and GMTs for all vaccine antigens indicated strong immune responses after each dose of the two vaccines, suggesting enhanced protection post-dose-2. Studies have reported similar results in the assessment of the MMRV vaccine in German children aged 11–21 mo and Singaporean children aged 9 mo. The strong increase in anti-varicella antibodies post-dose-2 in both vaccine groups is well-documented. This is especially encouraging as it supports the two-dose schedule for varicella vaccine in providing better long-term protection against the disease in young children.

Both vaccines were well-tolerated and had clinically acceptable safety profiles, as reported previously. The incidence of fever during the 15-d period after dose-1 indicated no difference between the MMRV new WS and MMRV vaccines. The peak prevalence of fever between days 5 and 12 post-dose-1 is characteristic of measles-containing vaccines, typically described during the second week post-vaccination. Moreover, the majority of cases reported for fever were low grade in intensity after each vaccine dose in both groups.

Table 2. Incidence of solicited local symptoms reported during the 4-d follow-up period in groups MMRV_new WS and MMRV (Total vaccinated cohort)

| Symptom   | Dose    | Type                  | MMRV_new WS group (Dose-1 n = 330; Dose-2 n = 327) | MMRV group (Dose-1 n = 166; Dose-2 n = 164) |
|-----------|---------|-----------------------|--------------------------------------------------|-----------------------------------------------|
|           |         |                       | % (95% CI)                                       | % (95% CI)                                   |
| Pain      | Post-dose-1 | Any                  | 18.8 (14.7; 23.4)                                 | 16.9 (11.5; 23.4)                           |
|           |         | Grade 3               | 0.0 (0.0; 1.1)                                    | 0.0 (0.0; 2.2)                               |
|           | Post-dose-2 | Any                  | 14.1 (10.5; 18.3)                                 | 14.6 (9.6; 21.0)                             |
|           |         | Grade 3               | 0.0 (0.0; 1.1)                                    | 0.0 (0.0; 2.2)                               |
| Redness   | Post-dose-1 | Any                  | 27.9 (23.1; 33.1)                                 | 26.5 (20.0; 33.9)                           |
|           |         | > 20 mm               | 0.6 (1.1; 2.2)                                    | 1.8 (0.4; 5.2)                              |
|           | Post-dose-2 | Any                  | 24.2 (19.6; 29.2)                                 | 26.2 (19.7; 33.6)                           |
|           |         | > 20 mm               | 1.2 (0.3; 3.1)                                    | 3.0 (1.0; 7.0)                              |
| Swelling  | Post-dose-1 | Any                  | 6.7 (4.2; 9.9)                                    | 6.6 (3.4; 11.5)                             |
|           |         | > 20 mm               | 0.0 (0.0; 2.1)                                    | 0.0 (0.0; 2.1)                              |
|           | Post-dose-2 | Any                  | 11.3 (8.1; 15.3)                                  | 12.2 (8.1; 17.7)                            |
|           |         | > 20 mm               | 0.3 (0.0; 1.7)                                    | 0.0 (0.0; 2.1)                              |

MMRV_new WS, measles-mumps-rubella-varicella vaccine derived from newly established working seed virus stock; MMRV: measles-mumps-rubella-varicella vaccine derived from current working seed virus stock; N, number of children with at least one documented dose; %, Percentage of children reporting the symptom at least once; 95% CI, Exact 95% confidence interval.

Discussion

The depletion of the current working seed virus stock justified the need for a new working seed virus stock. This study compared the immunogenicity and safety of a first dose of MMRV_new WS vaccine to that of the MMRV vaccine when administered to healthy Taiwanese and Singaporean children. The results demonstrated that immune responses to measles, mumps, rubella and varicella post-dose-1 of MMRV_new WS vaccine were non-inferior to that elicited by the MMRV vaccine. The primary non-inferiority criterion of ruling out a 10% difference in seroconversion rates post-dose-1 of MMRV_new WS compared with MMRV was achieved for all antigens.

The observed seroconversion rates and GMTs for all vaccine antigens indicated strong immune responses after each dose of the two vaccines, suggesting enhanced protection post-dose-2. Studies have reported similar results in the assessment of the MMRV vaccine in German children aged 11–21 mo and Singaporean children aged 9 mo. The strong increase in anti-varicella antibodies post-dose-2 in both vaccine groups is well-documented. This is especially encouraging as it supports the two-dose schedule for varicella vaccine in providing better long-term protection against the disease in young children.

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Both vaccines were well-tolerated and had clinically acceptable safety profiles, as reported previously. The incidence of fever during the 15-d period after dose-1 indicated no difference between the MMRV_new WS and MMRV vaccines. The peak prevalence of fever between days 5 and 12 post-dose-1 is characteristic of measles-containing vaccines, typically described during the second week post-vaccination. Moreover, the majority of cases reported for fever were low grade in intensity after each vaccine dose in both groups.

A vaccine-related febrile convulsion was reported in one child from the MMRV_new WS group, post-dose-2. Previous studies have indicated an increased risk of febrile convulsions in children administered with an initial dose of combined MMRV vaccine (Merck and Co., Inc., USA) specifically between 5–12 d or 7–10 d post-vaccination, as compared with co-administered MMR+V vaccines. A similar risk of febrile convulsions can be
One vaccine-related SAE occurred: norovirus infection coupled with seizure. However, norovirus gastroenteritis has previously been reported to be a significant cause of diarrhea-associated benign infant seizures.28

Our study results demonstrated non-inferiority of the immune responses elicited by the MMRV new WS vaccine to that elicited by the MMRV vaccine. The MMRV new WS vaccine was found to be generally well tolerated in Taiwanese and Singaporean children.

### Materials and Methods

#### Study design and children.
This phase II, randomized, double-blind study (NCT00892775) was conducted at multiple centers in Singapore and Taiwan between June 2009 and December 2010. Healthy children aged 11–22 mo were randomized (2:1) to expected with this study’s MMRV vaccine since a recent study has reported comparable fever profiles between GlaxoSmithKline’s and Merck’s combined MMRV vaccines.25 Higher rates of fever have also been reported with the study MMRV vaccine compared with co-administration of MMR+V. 17-19 Given this concern, the American Academy of Pediatrics recommends the use of either single dose co-administration of MMR+V or combined MMRV vaccine in children 12–47 mo of age.24 In cases where MMRV usage is being considered, the benefits and risks associated with the vaccine need to be conveyed to parents/guardians.26 Although the incidence of febrile convulsions is low in the present study, it is important to note that this study excluded children with a history of neurologic disease and seizures.27 Inclusion of such children may have resulted in a higher number of reported febrile seizures in this study.
receive two doses of either the MMRV vaccine derived from new working seed viruses (MMRV<sub>new WS</sub> group) or the MMRV vaccine derived from current working seed viruses (MMRV group). Due to expiry of the initial vaccine lots, 46 children (30 in the MMRV<sub>new WS</sub> group; 16 in the MMRV group) received commercially available MMRV vaccine as a second dose.

Children were excluded from participation if they had received any investigational drug/vaccine 30 d before the study vaccine or immunosuppressive medication/immunoglobulins/blood products six months before the study. A history of allergy likely to be aggravated by any of the vaccine constituents, neurological disease or seizures, chronic illness or family history of immunodeficiency or symptoms of acute illness at the time of enrollment were reasons for exclusion. Vaccination was postponed for children with a rectal temperature ≥ 38.0°C or an axillary temperature ≥ 37.5°C. Finally, children were excluded if they lived in a household with newborn infants, pregnant women with a negative history of chickenpox or immunodeficient people.

The study was conducted according to Good Clinical Practice, the Declaration of Helsinki and applicable rules and regulations of Taiwan and Singapore. Each participating center’s Independent Ethics Committee reviewed and approved all study-related documents. Parents/guardians provided written informed consent before executing any study-related procedures.

Study vaccines. The study vaccines, MMRV<sub>new WS</sub> and MMRV, were manufactured by GlaxoSmithKline, Belgium (Table 4). The vaccines were supplied in monodose vials, each containing a lyophilized pellet which was reconstituted with the diluent (provided in a pre-filled syringe) as a 0.5 ml dose before subcutaneous injection in the upper arm (deltoid region).

Immunogenicity assessment. Blood samples were collected at pre-vaccination and 43 d after each dose. Antibody titers were measured using commercial enzyme-linked immunosorbent assays (ELISA) – (Enzygnost<sup>TM</sup>, Dade Behring, Marburg, Germany) with cut-off values of 150 mIU/mL, 231 U/mL and 4 IU/mL for measles, mumps and rubella, respectively. For varicella, antibody titers were measured using an immunofluorescence assay (IFA) – (Virgo<sup>TM</sup>, Hemagen Diagnostics, Columbia, MD USA) (cut-off value of 4 dilution<sup>−1</sup>). The primary endpoint was based on immune responses following dose-1 of both vaccines. Additionally, antibody titers against varicella using ELISA (cut-off = 25 mIU/mL) were measured.

Safety/Reactogenicity assessment. Parents/guardians used diary cards to record the occurrence of solicited local symptoms (pain, redness and swelling) at the injection site for 4 d after each dose and solicited general symptoms [fever (axillary temperature ≥ 37.5°C/rectal temperature ≥ 38.0°C), rash/exanthem, parotid/salivary gland swelling and any suspected signs of meningism, including febrile convulsions] for 43 d after each dose. Body temperature was measured daily via the rectal/axillary route for the first 15 d after each vaccination. Between days 15 and 43, the presence of fever was assessed using a temperature-sensitive pad, and if fever was suspected, an accurate measurement of temperature was performed with a thermometer. Unsolicited symptoms were recorded for 43 d after each dose and serious adverse events (SAEs) were recorded throughout the study.

Intensity of symptoms was graded on a scale of 0–3. Grade 3 solicited symptoms were defined as: pain: when limb was moved or a spontaneously painful limb; redness and swelling: injection site surface diameter > 20 mm; fever: axillary temperature > 39°C or rectal temperature > 39.5°C; rash: > 150 lesions. Unsolicited symptoms (including SAEs) were defined as grade 3 when preventing normal daily activity.

Statistical analyses. All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.2, and 95% confidence intervals (CI) were calculated using Proc StatXact 8.1. The sample size was estimated taking into consideration the primary non-inferiority objective. Non-inferiority was achieved if the lower limit of the two-sided standardized asymptotic 95% CI for the difference in seroconversion rates between the two groups (MMRV<sub>new WS</sub> minus MMRV) was above -10% for each vaccine antigen, post-dose-1. A sample size of 498 children (332 in the MMRV<sub>new WS</sub> group; 166 in the MMRV group) was adequate to achieve power of at least 93.4%. A randomized (2:1) blocking scheme ensured that the balance between treatments was maintained by providing a unique treatment number that identified the vaccine dose to be administered to the children.

The immunogenicity analysis was performed on the ATP cohort, which included all children for whom pre- and post-dose-1 vaccination serology results were available, who were seronegative for at least one vaccine antigen before vaccination and who complied with study procedures. Seroconversion rates and geometric mean titers (GMTs) were calculated with exact 95% CIs for antibodies against each vaccine antigen after each dose. Seroconversion was defined as the appearance of antibodies (i.e., antibody concentration/titer ≥ cut-off value) in the serum of children who were seronegative before vaccination. The 95% CIs for the GMTs were obtained by exponential transformation of the 95% CI for the mean of log-transformed titer.

The safety analysis was performed on the total vaccinated cohort which included all vaccinated children. Solicited and unsolicited symptoms reported within their respective

### Table 4. Composition of study vaccines

| Vaccine          | Minimum viral titer after reconstitution |
|------------------|-----------------------------------------|
| MMRV<sub>new WS</sub> | 10<sup>13</sup> ≥ 10<sup>14</sup> ≥ 10<sup>13</sup> ≥ 10<sup>11</sup> |
| MMRV            | 10<sup>10</sup> ≥ 10<sup>17</sup> ≥ 10<sup>10</sup> ≥ 10<sup>11</sup> |

CCID<sub>50</sub> median cell culture infective dose; PFU, plaque-forming units.

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post-vaccination periods were tabulated with exact 95% CI. All SAEs reported throughout the study were described.

Disclosure of Potential Conflicts of Interest

L.M.H. and L.B.W. declare to have received payment for consultancy for being on the advisory board and their institutions received grants to conduct clinical trials, authors (L.M.H., L.B.W. and C.P.C.) declare either they/institution received payment for lectures including service on speakers bureaus and support for travel to meetings for the study or other purposes. M.P. and O.H. are employed by the GlaxoSmithKline group of companies.

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Figure 2. Prevalence of fever (any intensity) during the 43-d follow-up period after the first dose (Total vaccinated cohort). MMRV<new WS> measles-mumps-rubella-varicella vaccine derived from newly established working seed virus stock. MMRV, combined measles-mumps-rubella-varicella vaccine derived from current working seed virus stock.

Virgo is a registered trademark of Hemagen Diagnostics, Columbia, MD USA. Enzygnost is a registered trademark of Dade Behring, Marburg, Germany.
16. Rentier B, Gershon AA; European Working Group on Varicella. Consensus varicella vaccination of healthy children—a challenge for Europe. Pediatr Infect Dis J 2004; 23:379-89; PMID:15131459; http://dx.doi.org/10.1097/01.inf.0000122560.68429.8f.

17. Nolan T, McIntyre P, Robertson D, Descamps D. Reactogenicity and immunogenicity of live attenuated tetravalent measles-mumps-rubella-varicella (MMRV) vaccine. Vaccine 2002; 21:281-9; PMID:12450703; http://dx.doi.org/10.1016/S0264-410X(02)00459-0.

18. Kneif M, Habermuhl P, Zepp F, Mannhardt W, Kurrig M, Mustonen P, et al. Immunogenicity and safety of two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. Pediatr Infect Dis J 2006; 25:12-8; PMID:16395096; http://dx.doi.org/10.1097/01.inf.0000195626.35239.58.

19. Schuster V, Otto W, Maurer L, Tcherepniene P, Pfletschinger U, Kindler K, et al. Immunogenicity and safety assessments after one and two doses of a refrigerator-stable tetravalent measles-mumps-rubella-varicella vaccine in healthy children during the second year of life. Pediatr Infect Dis J 2008; 27:274-30; PMID:18600190; http://dx.doi.org/10.1097/INF0b013e3181770b22.

20. Rümke HC, Loech HP, Hoppenbrouwers K, Vandermeulen C, Malfoutor A, Helm K, et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine 2011; 29:3842-9; PMID:21382484; http://dx.doi.org/10.1016/j.vaccine.2011.02.067.

21. Goh P, Lim FS, Han HH, Willems P. Safety and immunogenicity of early vaccination with two doses of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine in healthy children from 9 months of age. Infection 2007; 35:266-33; PMID:17710370; http://dx.doi.org/10.1007/s15010-007-6357-z.

22. Centers for disease control and prevention. Measles. In: Atkinson W, Hamborsky J, McIntyre L, Wolfe S, (eds.): Epidemiology and prevention of vaccine-preventable diseases (9th edn). Public Health Foundation, Washington DC, 2006; 125-44.

23. Jacobson SL, Ackerson BK, Sy LS, Tran TN, Jones TL, Yao JE, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009; 27:4656-61; PMID:19520201; http://dx.doi.org/10.1016/j.vaccine.2009.05.056.

24. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al.; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010; 126:e1-8; PMID:20587679; http://dx.doi.org/10.1542/peds.2010-0665.

25. Blatter MM, Klein NP, Shepard JS, Leonard M, Shapiro S, Schear M, et al. Immunogenicity and safety of two tetravalent (measles, mumps, rubella, varicella) vaccines coadministered with hepatitis a and pneumococcal conjugate vaccines to children twelve to fourteen months of age. Pediatr Infect Dis J 2012; 31:e133-40; PMID:22622099; http://dx.doi.org/10.1097/INF.0b013e318259fca8.

26. Committee on Infectious Diseases. Policy statement—Prevention of varicella: update of recommendations for use of quadrivalent and monovalent varicella vaccines in children. Pediatrics 2011; 128:630-2; PMID:21873692; http://dx.doi.org/10.1542/peds.2011-1968.

27. Berg AT, Shinnar S, Hauser WA, Alemany M, Shapiro ED, Salomon ME, et al. A prospective study of recurrent febrile seizures. N Engl J Med 1992; 327:1122-7; PMID:1528207; http://dx.doi.org/10.1056/NEJM199210153271603.

28. Chen SY, Tsai CN, Lai MW, Chen CY, Lin KL, Lin TY, et al. Norovirus infection as a cause of diarrhea-associated benign infantile seizures. Clin Infect Dis 2009; 48:849-55; PMID:19239351; http://dx.doi.org/10.1086/597256.