RESEARCH PAPER

# Safety and Immunogenicity of Two Doses of a Quadrivalent Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Indian and Russian Children Aged 9 to 17 Months

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**Objective:** Evaluation of tolerability, safety and immunogenicity of a two-dose series of a quadrivalent meningococcal polysaccharide diptheria toxoid conjugate (ACYW-D) vaccine in Indian and Russian infants/toddlers.

**Design:** Open-label, single-arm, phase III multi-national trial.

**Study participants:** 300 children aged 9-17 months, previously unvaccinated against meningococcal disease from four sites each in India (*n*=200) and the Russian Federation (*n*=100).

**Intervention:** Two 0.5 mL doses of ACYW-D by intramuscular injection, 3-6 months apart.

**Main outcome measures:** Meningococcal antibody titers to serogroups A, C, W-135 and Y, determined using a serum bactericidal assay in the presence of human complement before vaccination and 28 days after the second vaccination. Titers ≥1:8 against either/all of the A, C, W-135 or Y were considered seroprotective.

**Results:** After dose 2, 95.7–99.5% and 92.9–99.0% of infants/toddlers achieved seroprotection across the four serogroups in India and the Russian Federation, respectively. No immediate adverse events were reported after any dose of ACYW-D. Solicited reactions were reported in 49.2% of participants, and were mainly of Grade 1 severity, and resolved within three days. Unsolicited adverse events were reported in 19.1% of infants: one event (Grade 3 diarrhea, resolving within one day) was considered related to study vaccine. No non-serious adverse events led to premature withdrawal from the study. Four serious adverse events were reported; none were considered related to study vaccine. No deaths occurred during the study.

**Conclusions:** A two-dose series of ACYW-D vaccine in Indian and Russian children (9-17 month) was well-tolerated with no safety concerns, and induced robust bactericidal antibody responses against the meningococcal serogroups contained in the vaccine.

**Keywords:** *Bactericidal assay, Immunization, Meningococcus, Prevention.*

**Clinical Trial Registration**: CTRI/2014/12/005272 and NCT01890759.

Rates of meningococcal disease vary from <1-3/100,000 in developed countries to 10-25/100,000 in less developed countries [1]. Invasive meningococcal disease (IMD) is estimated to cause death in 10-15% of cases [2]. The majority of IMD cases in the Russian Federation occur in children aged up to 2 years, with an incidence of approximately 14/100,000 [3, 4]. In the Russian Federation, the incidence of meningococcal infection in 2007 was reported to have declined from 5.0 per 100,000 population in 1989 through to 1.9 cases per 100,000 population in 2007, but was 8-11/100,000 in children aged <14 years [3]. In India, meningococcal disease surveillance is not enforced [5-7] and several epidemics have been reported. Six meningococcus serogroups (A, B, C, W, X and Y) cause most cases of IMD [8, 9]. Strain A was associated with all major epidemics in India, with small numbers of serogroup C isolated in one epidemic [5]. In the Russian Federation, serogroups A, B and C are responsible for most IMD cases with serogroup A mainly responsible [10], and Y and W isolated in some cases.

The meningococcal (Groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine

(Men-ACYW-D; Menactra, Sanofi Pasteur) is approved for active immunization against IMD in >60 countries [11]. ACYW-D was licensed in the USA in 2005, and is approved for primary vaccination in children aged 9-23 months as a two-dose series, and in individuals aged 2-55 years as a single dose [12, 13]. A rabbit complement serum bactericidal antibody titer of ≥1:8 was validated to be seroprotective against serogroup C IMD [14].

When the present study started, no quadrivalent meningococcal conjugated vaccine was licensed for broad-based protection against IMD from early childhood (<2 years) in India or in the Russian Federation, but ACYW-D was licensed for those aged 2-55 years. Previous phase I/II studies showed this vaccine was immunogenic with a good safety profile in infants, toddlers and children [15, 16]. A phase III study was therefore performed to determine the proportion of Indian and Russian infants and toddlers achieving sero-protective titers after immunization with Men-ACYW-D vaccine, and assess any adverse events following immunization.

## METHODS

This was an open-label, single-arm, international phase III trial undertaken at four sites in the Russian Federation (between 25 June, 2013 and 9 April, 2014) and four sites in India (between 24 March, 2015 and 12 April, 2016). The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on the Harmonization – Good Clinical Practice, and was approved by the relevant Institutional Review Board and Independent Ethics Committee of each of the eight participating centers. Parents/legal guardians of all infants and toddlers participating in the study gave written informed consent for their child to participate, and were present at each study visit. There were four study visits on Day 0, Day 28-35, Day 90-180, and 28-35 days after the third visit.

Infants and toddlers from India and the Russian Federation aged 9-17 months at entry were eligible. Key exclusion criteria included a history (confirmed clinically, serologically, or microbiologically) or high risk (investigators opinion) of meningococcal disease, acute disease/infection (any severity at Russian sites or moderate to severe at Indian sites) according to the investigator or fever (axillary temperature ≥37.0°C at Russian sites, and temperature ≥38.0°C at Indian sites) on the day of vaccination, bleeding disorders or receipt of anticoagulants in the preceding three weeks, history of known thrombocytopenia, or immunodeficiency conditions. Those receiving immunosuppressive medication, or another vaccine (other than influenza or measles, mumps, rubella [MMR] vaccines, or oral poliomyelitis vaccine [OPV] at the Indian sites) in the four weeks before or after the study vaccination, or those previously vaccinated against meningococcal disease were also excluded.

Participants received two 0.5 mL doses of Men-ACYW-D by intramuscular injection (anterolateral thigh or optionally, deltoid muscle for toddlers aged ≥12 months). Dose 2 was given 3-6 months after Dose 1. Each 0.5 mL dose was formulated in sodium phosphate buffered isotonic sodium chloride solution to contain meningococcal capsular polysaccharides (A, C, Y, and W: 4 µg each) conjugated to approximately 48 µg of diphtheria toxoid protein.

Serum samples were collected immediately before Dose 1 and 28 days (+7 days) after Dose 2, frozen and maintained at –20°C until immunogenicity analysis at a central laboratory (Global Clinical Immunology, Sanofi Pasteur, Swiftwater, USA). Meningococcal antibody titers to serogroups A, C, W and Y were determined using the serum bactericidal assay in the presence of human complement (SBA-HC), expressed as SBA-HC geometric mean titers (GMTs) as previously described [12]. Antibody titers ≥1:8 were considered seroprotective for each serogroup; although a titer of 1:4 could be considered protective, the higher titer was chosen as a conservative assumption [17]. The number and percentage of participants who achieved a four-fold increase in titers 28 days after the second dose compared with pre-vaccination were calculated.

Safety was assessed by monitoring adverse reactions (ARs) or events (AEs). Participants were monitored for 30 minutes after each injection for any immediate ARs or AEs. In addition, solicited systemic (fever, vomiting, abnormal crying, drowsiness, loss of appetite and irritability) and local (pain, erythema, and swelling) ARs were recorded for the first seven days after either dose, and unsolicited AEs and ARs were recorded for the first 28 days after either dose. Diary cards were provided to parents or guardians on Visit 1, 2, and 3 to maintain a written record of AEs. Parents or guardians were contacted by telephone 8 days after each vaccination. Serious adverse events (SAEs) were recorded during the entire study period.

A sample size of 300 participants (India, 200; Russian Federation, 100) was arbitrarily chosen to ensure 180 evaluable participants from India and 90 from the Russian Federation, assuming an attrition rate of 10%.

*Statistical analyses*: Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, North

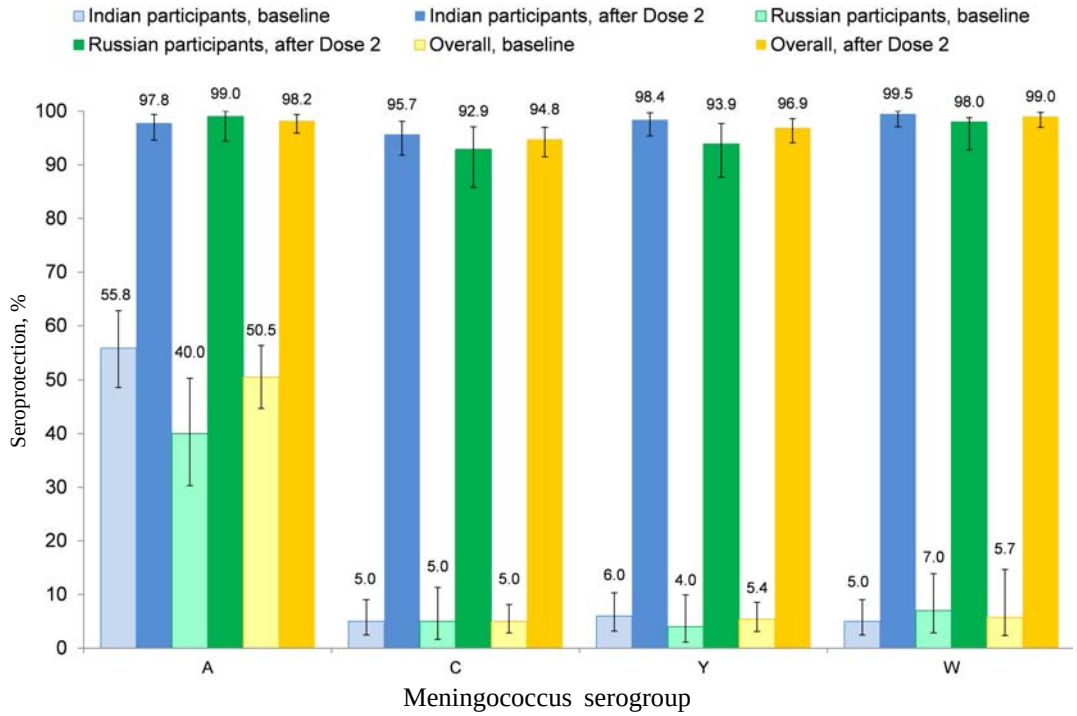


**FIG. 1** *Seroprotection (percentage of participants with SBA-HC titer ≥8 (1/dil) [95% confidence intervals]) at baseline and after Dose 2 (Full Analysis Set).*

Carolina, USA). All planned analyses were descriptive with no hypothesis testing. The full analysis set (FAS) consisted of all participants who received ≥1 dose of study vaccine; the safety analysis set consisted of all participants in the FAS with safety data available. To calculate the four-fold rises in titers 28 days after the second dose compared with pre-dose, any pre-dose 1 titer reported as <lower limit of quantification (LLOQ) was converted to a value equal to LLOQ, and any post-dose 2 titer reported as <LLOQ was converted to a value of 0.5 LLOQ. Any value >ULOQ was converted to the ULOQ to calculate the four-fold increases. Safety and reactogenicity were assessed on the safety analysis set; the incidences of AEs/ARs were calculated individually, by country, and overall.

## RESULTS

In total, 200 participants were enrolled at the sites in India and 100 in the Russian Federation. At baseline, 41.0% and 65.8% of participants were male, and the mean (standard deviation) age at entry was 13.5 (2.7) and 12.9 (3.0) months in the Russian Federation and Indian study, respectively. Of the Indian participants, 199 received Dose 1 and 191 received both doses. In total, 188 children completed the study; of the withdrawals, eight were by parental request, and four were by investigator decision. Of these four, two babies were excluded due to protocol deviations (one received Hepatitis B + OPV 27 days prior to inclusion; the other did not attend Visit 3), and two were lost to follow-up. All Russian participants received the first dose of Men-ACYW-D, and 98 received both doses of Men-ACYW-D and completed the study. Two children were withdrawn from the study before receiving Dose 2 due to parental request.

At baseline, in the full analysis set, seroprotection (SBA-HC titer of ≥8 [1/dil]) rates against meningococcus serogroup A (55.8% in India and 40% in Russia) were higher than for the other serogroups (range 4-7% in both countries; ***Fig.* 1**). After Dose 2, 92.9-99.0% and 95.7-99.5% of children achieved seroprotection across the four serogroups in the Russian Federation and India, respectively. In addition, 86.5-97.3% and 80.6-90.8% of participants in India and Russia, respectively, had a ≥4-fold increase from baseline to post-Dose 2 in SBA-HC titers across the four serogroups.

Rates of seroprotection and geometric mean SBA-HC titers by serogroup in India and the Russian Federation are given in ***Table* I**. SBA-HC GMTs post-Dose 2 were markedly higher than at baseline for all serogroups.

No immediate ARs or AEs were reported after any dose of Men-ACYW-D. Solicited reactions occurred in 49.2% of children (***Table* II**). Most solicited injection site

**TABLE I** RATES OF SEROPROTECTION AND GEOMETRIC MEAN SBA-HC TITERS BY SEROGROUP IN INDIA AND THE RUSSIAN FEDERATION (FULL ANALYSIS SET)

| | *India* | | *Russian Federation* | |
|---|---|---|---|---|
| | *Proportion (%) of participants with seroprotection (95% CI)* | *GM (95% CI)* | *Proportion (%) of participants with seroprotection (95% CI)* | *GM (95% CI)* |
| *Serogroup A* | | | | |
| Pre-Dose 1 (baseline) | 55.8 (48.6-62.8) | 6.77 (6.00-7.63) | 40.0 (30.3-50.3) | 5.43 (4.76-6.18) |
| Post-Dose 2 | 97.8 (94.6-99.4) | 101 (83.1-122) | 99.0 (94.4-100) | 142 (108-188) |
| Post-Dose 2 response *vs* pre-Dose 1 | 86.5 (80.7-91.1) | 14.8 (11.7-18.9) | 90.8 (83.3-95.7) | 25.9 (19.1-35.1) |
| *Serogroup C* | | | | |
| Pre-Dose 1(baseline) | 5.0 (2.44-9.05) | 2.46 (2.19-2.77) | 5.0 (1.64-11.3) | 2.39 (2.19-2.62) |
| Post-Dose 2 | 95.7 (91.8-98.1) | 138 (111-171) | 92.9 (85.8-97.1) | 59.6 (42.7-83.2) |
| Post-Dose 2 response *vs* pre-Dose 1 | 92.6 (87.8-95.9) | 55.4 (43.2-71.1) | 80.6 (71.4-87.9) | 24.8 (17.6-34.9) |
| *Serogroup Y* | | | | |
| Pre-Dose 1(baseline) | 6.0 (3.15-10.3) | 2.44 (2.17-2.75) | 4.0 (1.10-9.93) | 2.30 (2.05-2.57) |
| Post-Dose 2 | 98.4 (95.4-99.7) | 106 (86.8-129) | 93.9 (87.1-97.7) | 55.6 (42.7-72.3) |
| Post-Dose 2 response *vs* pre-Dose 1 | 93.1 (88.5-96.3) | 43.3 (34.4-54.5) | 89.8 (82.0-95.0) | 24.1 (17.9-32.5) |
| *Serogroup W-135* | | | | |
| Pre-Dose 1(baseline) | 5.0 (2.44-9.05) | 2.43 (2.15-2.75) | 7.0 (2.86-13.9) | 2.46 (2.14-2.83) |
| Post-Dose 2 | 99.5 (97.1-100) | 202 (169-242) | 98.0 (92.8-99.8) | 99.9 (79.9-125) |
| Post-Dose 2 response *vs* pre-Dose 1 | 97.3 (93.9-99.1) | 82.5 (66.6-102) | 89.8 (82.0-95.0) | 40.4 (30.7-53.3) |

*Seroprotection, an antibody titer ≥1:8 dilution against each serogroup; CI, confidence interval, GM, geometric mean; SBA-HC, serum bactericidal assay with human complement.*

**TABLE II** SAFETY OVERVIEW AFTER ANY STUDY VACCINE INJECTION (PERCENTAGE OF PARTICIPANTS EXPERIENCING ≥1 EVENT) IN THE INDIAN AND RUSSIAN FEDERATION STUDIES: SAFETY ANALYSIS SETS

| | *India (n=199)* | *Russian Federation (n=100)* | *Overall (n=299)* |
|---|---|---|---|
| Immediate unsolicited AE/AR, *n* (%) | 0 | 0 | 0 |
| Solicited reaction, *n* (%) | 86 (43.2) | 61 (61.0) | 147 (49.2) |
| Injection site reaction, *n* (%) | 43 (21.6) | 45 (45.0) | 88 (29.4) |
| Systemic reaction, *n* (%) | 72 (36.2) | 40 (40.0) | 112 (37.5) |
| Unsolicited AE, *n* (%) | 47 (23.6) | 10 (10.0) | 57 (19.1) |
| Non-serious systemic AE, *n* (%) | 46 (23.1) | 9 (9.0) | 55 (18.4) |
| Unsolicited AR, *n* (%) | 0 | 1 (1.0) | 1 (0.3) |
| Non-serious injection site AR, *n* (%) | 0 | 0 | 0 |
| Non-serious systemic AR, *n* (%) | 0 | 1 (1.0) | 1 (0.3) |
| SAEs, *n* (%) | 3 (1.5) | 1 (1.0) | 4 (1.3) |
| Death, *n* (%) | 0 | 0 | 0 |

*AE: adverse event; AR: adverse reaction; SAE: serious adverse event.*

**WHAT IS ALREADY KNOWN?**

- The Men-ACYW-D vaccine has a good safety and immunogenicity profile.

**WHAT THIS STUDY ADDS?**

- A high proportion of infants and toddlers in India and the Russian Federation achieve seroprotective titers following Men-ACYW-D in a 2-dose schedule 3–6 months apart.

**TABLE III** PERCENTAGES OF PARTICIPANTS EXPERIENCING ≥1 UNSOLICITED AE AFTER ANY STUDY VACCINE INJECTION (MOST COMMON AES, ≥1% IN OVERALL POPULATION) IN THE INDIA AND RUSSIAN FEDERATION STUDIES: SAFETY ANALYSIS SETS

| | *India (n=199)* | *Russian Federation (n=100)* | *Overall (n=299)* |
|---|---|---|---|
| Diarrhea, n (%) | 9 (4.5) | 1 (1.0) | 10 (3.3) |
| Vomiting, *n* (%) | 2 (1.0) | 1 (1.0) | 3 (1.0) |
| Pyrexia, *n* (%) | 7 (3.5) | 1 (1.0) | 8 (2.7) |
| Nasopharyngitis, *n* (%) | 3 (1.5) | 4 (4.0) | 7 (2.3) |
| Respiratory tract infection, *n* (%) | 7 (3.5) | 2 (2.0) | 9 (3.0) |
| Upper respiratory tract infection, *n* (%) | 10 (5.0) | 0 | 10 (3.3) |
| Viral respiratory tract infection, *n* (%) | 3 (1.5) | 0 | 3 (1.0) |
| Cough, *n* (%) | 9 (4.5) | 1 (1.0) | 10 (3.3) |

*AE, adverse event.*

reactions and solicited systemic reactions occurred during the three days after injection, were of Grade 1 severity, and resolved within three days. Unsolicited ARs after any study injection were very infrequent (***Table* II**). Unsolicited AEs were reported in approximately 20% of all children (***Table* II**). The most common unsolicited AEs reported occurred at a rate ≤5% (***Table* III**). One unsolicited non-serious AE (Grade 3 diarrhea at a Russian site, which resolved within one day) was considered by the investigator to be related to the study vaccine. Two other cases of unsolicited non-serious AEs (rhinitis at a Russian site and fever at an Indian site) were of Grade 3 severity. No non-serious AEs led to premature withdrawal from the study.

Four SAEs were reported; one at a Russian site and three at Indian sites: nasopharyngitis, acute respiratory tract infection, lower respiratory tract infection, and forearm abscess (mosquito bite complication at a site unrelated to vaccine injection), which all required hospitalization. None was considered related to study vaccine by the investigators. No deaths occurred during the study.

## DISCUSSION

These studies show that a two-dose series of Men-ACYW-D vaccine administered 3-6 months apart is well tolerated with no safety concerns, and induces seroprotective titers against each of the four meningococcal serogroups in ≥93% of Russian and Indian children aged 9-17 months. These results are consistent with other studies of Men-ACYW-D in the similar age groups [12,18,19], and in older age groups [11, 20].

The baseline GMTs for group A were high compared with Groups C, Y, and W. This may have been due to the serum bactericidal assay utilized and not due to the higher baseline seroprevalence of Group A.

A two-dose series of Men-ACYW-D in infants and toddlers would benefit management of IMD in the Russian Federation and India, as the highest incidence rates registered or cases reported in these areas are among children aged up to two years of age and <5 years, respectively [1,3-5]. It has been previously shown that Men-ACYW-D induces a robust protective immune response and is generally well tolerated when administered with other routine pediatric vaccines; concomitant use does not adversely affect the immunogenicity of either vaccine or their relative safety profiles [17,19]. Limitations of the study include the unblinded, non-comparative design of the trial and lack of appropriate controls. As this was a descriptive study and there were no statistically powered hypotheses, the number of participants was arbitrarily chosen. In

addition, the study was not designed or powered to compare differences in immunogenicity data between the two countries and no clinical efficacy data were obtained; as such, it is not meaningful to directly compare the respective data presented. This study was intended as confirmatory only, on the basis of existing supportive evidence and approval in many countries.

In conclusion, our results with Men-ACYW-D are consistent with previous studies in young children, and support efficacy and safety in infants and toddlers in India and the Russian Federation.

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## REFERENCES

1. Manchanda V, Gupta S, Bhalla P. Meningococcal disease: History, epidemiology, pathogenesis, clinical manifestations, diagnosis, antimicrobial susceptibility and prevention. Indian J Med Microbiol. 2006;24:7-19.
2. Pace D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. Vaccine. 2012;30:062.
3. Titova L, Samodova O, Buzinov R, Gordienko T. Epidemiology of meningococcal infection in arkhangelsk-oblast. Available from: *http://wwwepinorthorg/eway/defaultaspx?pid=230&trg=Area_5268&MainArea_5260=5263:0:15,2946:1:0:0:::0:0&Area_5263=5268:44984::1:5264: 1:::0:0&Area_5268=5273:47185::1:5266:3:::0:0.* Accessed June 19, 2017.
4. Koroleva IS, Maxina TA, Zakroeva M, Beloshitsky GV, Lytkina IN, Pyaeva AP. Epidemiology of invasive meningococcal disease in Moscow, 2005-2010. Available from: *www.meningitis.org/assets/x/53942.* Accessed June 19, 2017.
5. Sinclair D, Preziosi MP, Jacob John T, Greenwood B. The epidemiology of meningococcal disease in India. Trop Med Int Health. 2010;15:1421-35.
6. John TJ, Gupta S, Chitkara AJ, Dutta AK, Borrow R. An overview of meningococcal disease in India: knowledge gaps and potential solutions. Vaccine. 2013;31:2731-7.
7. Borrow R, Lee JS, Vazquez JA, Enwere G, Taha MK, Kamiya H, *et al*. Meningococcal disease in the Asia-Pacific region: Findings and recommendations from the Global Meningococcal Initiative. Vaccine. 2016;34: 5855-62.
8. Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, *et al*. Global epidemiology of invasive meningococcal disease. Popul Health Metr. 2013;11:17.
9. Borrow R, Alarcon P, Carlos J, Caugant DA, Christensen H, Debbag R, *et al*. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines. 2017;16:313-28.
10. Koroleva I, Beloshitskij G, Zakroeva I, Melnikova A, Koroleva M, Shipulin G, *et al*. Invasive meningococcal disease in Russian Federation. In: European Meningococcal Disease Society. 20 years EMGM. Bad Loipersdorf, Austria. 17-19 September 2013. p71. A*vailable from: http://emgm.eu/meetings/emgm2013/Abstract_Book_EMGM_2013.pdf.* Accessed April 13, 2017.
11. Robertson CA, Greenberg DP, Hedrick J, Pichichero M, Decker MD, Saunders M. Safety and immunogenicity of a booster dose of meningococcal (groups A, C, W, and Y) polysaccharide diphtheria toxoid conjugate vaccine. Vaccine. 2016;34:5273-8.
12. Pina LM, Bassily E, Machmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and toddlers: three multicenter phase III studies. Pediatr Infect Dis J. 2012; 31:1173-83.
13. Pelton SI, Gilmet GP. Expanding prevention of invasive meningococcal disease. Expert Rev Vaccines. 2009;8: 717-27.
14. Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection – serum bactericidal antibody activity. Vaccine. 2005;23:2222-7.
15. Choudhuri D, Huda T, Theodoratou E, Nair H, Zgaga L, Falconer R, *et al*. An evaluation of emerging vaccines for childhood meningococcal disease. BMC Public Health. 2011;11:S29.
16. Halperin SA, Diaz-Mitoma F, Dull P, Anemona A, Ceddia F. Safety and immunogenicity of an investigational quadrivalent meningococcal conjugate vaccine after one or two doses given to infants and toddlers. European J Clin Microb Infect Dis. 2010;29:259-67.
17. Santos GF, Deck RR, Donnelly J, Blackwelder W, Granoff DM. Importance of complement source in measuring meningococcal bactericidal titers. Clin Diagn Lab Immunol. 2001;8:616-23.
18. Hansen J, Zhang L, Eaton A, Baxter R, Robertson CA, Decker MD, *et al*. Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine (MenACWY-D) in infants and children. Vaccine. 2018;36:2133-8.
19. Noya F, McCormack D, Reynolds DL, Neame D, Oster P. Safety and immunogenicity of two doses of quadrivalent meningococcal conjugate vaccine or one dose of meningococcal group C conjugate vaccine, both administered concomitantly with routine immunization to 12- to 18-month-old children. Can J Infect Dis Med Microbiol. 2014;25:211-6.
20. Yadav S, Manglani MV, Narayan DA, Sharma S, Ravish HS, Arora R, *et al*. Safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine (MenACYW-DT): a multicenter, open-label, non-randomized, phase III clinical trial. Indian Pediatr. 2014; 51:451-6.