Original Article
http://dx.doi.org/10.3947/ic.2016.48.1.12
Infect Chemother 2016;48(1):12-19
ISSN 2093-2340 (Print) · ISSN 2092-6448 (Online)

Infection & Chemotherapy

A Survey of Serum Bactericidal Antibodies against *Neisseria meningitidis* Serogroups A, C, W and Y in Adolescents and Adults in the Republic of Korea

Jin-Han Kang[1], Yan Miao[2], SooYoung Lee[3], Jong-Hyun Kim[4], Kyung-Yil Lee[5], Sang Hyuk Ma[6], Dae Sun Jo[7], HyoYoung Song[8], and Mendel Haag[9]

[1]Department of Pediatrics, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea; [2]GlaxoSmithKline BV, Amsterdam, The Netherlands; [3]Department of Pediatrics, Incheon St.Mary's Hospital, The Catholic University of Korea, Incheon; [4]Department of Pediatrics, St. Vincent's Hospital, The Catholic University of Korea, Suwon; [5]Department of Pediatrics, Daejeon St. Mary's Hospital, The Catholic University of Korea, Daejeon; [6]Department of Pediatrics, Changwon Fatima Hospital, Changwon; [7]Department of Pediatrics, Chonbuk National University Hospital, Chonbuk National University Medical School, Jeonju; [8]Novartis Korea Ltd, Seoul, Korea; [9]Seqirus Netherlands BV, Amsterdam, the Netherlands

Background: This descriptive epidemiological study aimed to assess the prevalence of serum bactericidal antibodies against *Neisseria meningitidis* serogroups A, C, W and Y in adolescents and adults in the Republic of Korea.

Materials and Methods: In total, 987 subjects aged 11-55 years from five geographical regions of Korea were included in the study. Human serum bactericidal assay (hSBA) was used to measure hSBA titres for serogroups A, C, W and Y. Percentages of subjects with hSBA titres ≥4 and ≥8, geometric mean titres (GMTs), and associated 95% confidence intervals (CIs), were estimated. Analysis was performed for the entire study population and stratified by age group or region. No statistical hypotheses were tested.

Results: The highest percentage of subjects with hSBA titres ≥8 was observed for serogroup W (74%), was similar for serogroups C (34%) and Y (36%), and was lowest for serogroup A (9%). The percentages of subjects with hSBA titres ≥4 were similar to those with hSBA titres ≥8 for all serogroups. GMTs were 2.56 μg/mL (serogroup A), 5.14 μg/mL (serogroup C), 22.63 μg/mL (serogroup W) and 5.28 μg/mL (serogroup Y). Similar trends in GMTs across serogroups were seen for individual regions and age groups. The highest GMTs for serogroups A, W and Y were recorded in the >19-29 years group, and for serogroup C in the >49-55 years group. Across all regions, GMTs were very similar for serogroups A, C and Y, while more variation was seen for serogroup W.

Conclusion: In the Korean population, among *Neisseria meningitidis* serogroups A, C, W and Y, serum bactericidal antibodies were most prevalent against serogroup W and least prevalent against serogroup A. These trends were maintained across age groups and regions. The highest GMTs for serogroups A, W and Y were observed in the >19-29 years group. The reasons behind the observed differences in prevalence of bactericidal antibodies against the serogroups are currently not understood, although carriage and cross-reactivity of the assay may be important influences.

Key Words: Serosurveillance; *Neisseria meningitidis*; Republic of Korea; Adults; Adolescents; Epidemiology; hSBA; Serogroups

Received: August 3, 2015 **Revised:** January 15, 2016 **Accepted:** January 29, 2016

Corresponding Author : Yan Miao
GlaxoSmithKline BV, Hullenbergweg 83-85, 1101 CL Amsterdam, The Netherlands
Tel: +31-2-05640564, Fax: +31-2-05640565,
E-mail: yan.x.miao@gsk.com

Alternate Corresponding Author : Mendel Haag
Seqirus Netherlands BV, Hullenbergweg 83-85, 1101 CL Amsterdam, The Netherlands
Tel: +31-2-05640578
E-mail: mendel.haag@seqirus.com

Introduction

Neisseria meningitidis serogroups A, B, C, W, and Y are considered to be the main serogroups causing meningococcal disease, accounting for over 90% of cases worldwide [1]. Meningococcal disease has substantial morbidity and mortality, even in those receiving early antibiotic treatment [2]. Case fatality rates range from 5% to 10%, and survivors often suffer long-term sequelae such as limb loss or neurological problems [3].

The distribution of cases caused by different meningococcal serogroups varies geographically and temporally, and the disease can occur from sporadic cases up to large scale epidemics. The majority of cases occur in the "meningitis belt" of sub-Saharan African and since the introduction of an immunisation campaign against serogroup A in 2010, are now predominantly caused by serogroup W [4]. Serogroups B, C and Y are currently the predominant serogroups in North America, B and C in Europe, and A and C in Asia, although there have been few studies in the latter region [4-6]. In the Republic of Korea, meningococcal disease is considered a category 3 notifiable disease, with the possibility of intermittent outbreaks [7]. Although the burden of meningococcal disease in Korea is thought to be low, the number of reported cases fluctuates, with the most recent peak in 2002 and 2003, when 63 cases were reported [8]. Quadrivalent (ACWY) meningococcal vaccination is indicated for new recruits to the Korean army, but is not included in the National Immunisation Programme [9].

Worldwide, up to 10% of individuals in a population are thought to be carriers of *N. meningitidis* [10]. Carriage varies with age, with the highest carriage rates seen in adolescents and the lowest in infants [10]. In Korea, carriage rates have been estimated to be between 11% and 55%, depending on the study population [11, 12]. However, carriage rates and burden of disease are not correlated [13], and asymptomatic carriage tends to be an immunising event, leading to the production of bactericidal antibodies against the carried strain [1]. In a recent clinical trial of the quadrivalent MenACWY-CRM vaccine in adolescents and adults in Korea, a high proportion of subjects with baseline functional bactericidal antibodies against serogroup W was noted [14].

This descriptive epidemiological study aimed to investigate the prevalence of serum bactericidal antibodies against serogroups A, C, W and Y in adolescents and adults aged 11-55 years in five regions of Korea.

Materials and Methods

The study was conducted between May and November 2013 at six medical sites in the five main geographical regions of Korea (Seoul, Gyeonggi-do [2 sites], Jeolla-do, Chungcheong-do, and Gyeongsang-do). The protocol was approved by the institutional review boards for each site and the study was conducted in accordance with the principles of Good Clinical Practice, with local applicable regulations, and the ethical principles laid down in the Declaration of Helsinki. Prior to enrolment, written informed consent was obtained from each of the subjects (≥20 years), or from the subject's parent/legal guardian (11-19 years). Informed assent was also obtained where possible from subjects < 20 years.

Adolescents and adults between 11 and 55 years of age, who were generally in good health, or those with controlled non-serious chronic conditions, were included in the study. Subjects were excluded from enrolment if they were currently taking or had (within 7 days of screening) taken antibiotics, or had received a prior meningococcal vaccination or a vaccination containing meningococcal antigen. Additional exclusion criteria were uncontrolled/progressive or serious chronic illness, any condition associated with prolonged bleeding time or use of blood thinning medication, recent use of immunostimulants or immunosuppressive therapy (within 28 days), receipt of immunoglobulin or blood products (within 90 days) or known pregnancy.

At enrolment, a number of demographic variables were collected to allow for a description of the study population and to determine the prevalence of factors that may impact *N. meningitidis* antibody titres. These data included age, sex, ethnicity, region/city of main residence, highest level of education obtained, current employment/education status, number of members/children under 10 years sharing household, whether the subject lived in a dormitory residence or not. In addition, health status information such as concomitant medications, any current controlled non-serious conditions, and any previous self-reported meningococcal disease were recorded.

A single 10 mL blood sample was taken from each enrolled subject. Serum samples were prepared at site, stored at -18°C, and shipped to the Novartis Clinical Sciences Laboratory (Marburg, Germany) for analysis. Serum antibody titres for serogroups A, C, W and Y were measured using the human serum bactericidal assay (hSBA) [15]. For each of the serogroups, the percentage of subjects with hSBA titres ≥4 and ≥8, hSBA geometric mean titres (GMTs) and associated 95% confidence intervals (CI) were calculated. Data were analysed de-

scriptively for the entire study population, as well as by age group and by geographic region. For sub-group analysis by age group, data were split into five age strata (≥11-19 years, >19-29 years, >29-39 years, >39-49 years, >49-55 years). No formal statistical hypotheses were tested. The planned study size was 900 evaluable subjects, with equal distribution across age group and geographic region for sub-group analysis. Based on approximately 180 subjects in each subgroup and 55% of these subjects with an hSBA titre ≥4 or 8, the confidence interval around the point estimate would be 47.4-62.4%.

Results

The mean age of subjects in the study was 34 years (Table 1). All subjects were of Asian ethnicity. Sex distribution of the study participants differed between age groups, with approximately half of the adolescent age group (≥11-19 years) being male, and one quarter being male in the >39-49 years and >49-55 years age groups. Subject enrolment was evenly distributed across the five age groups and study regions. The majority of subjects obtained high school education or above, which is consistent with the general population trends in Korea [16]. In contrast to the population statistics, a higher percentage of subjects were unemployed (12%) than was reported for Korea in 2013 (3.2% for the 15-64 years age group), and the number of people sharing a household with less than three other people (approximately 15%) was lower than the

Table 1. Demographics of the study population. Data are presented as number of subjects (percentage in parenthesis) unless otherwise stated

Characteristic	N = 987
Demographics	
Mean age, yrs (±SD)	34.0 ± 13.4
Male	331 (34%)
Female	656 (66%)
Asian	987 (100%)
Region of main residency	
Seoul	134 (14%)
Gyeonggi-do	235 (24%)
Jeolla-do	200 (20%)
Chungcheong-do	199 (20%)
Gyeongsang-do	187 (19%)
Other	32 (3%)
Region of main residency same as region of site	872 (88%)
Age group (years)	
≥ 11-19	198 (20%)
> 19-29	198 (20%)
> 29-39	197 (20%)
> 39-49	197 (20%)
> 49-55	197 (20%)
Highest level of education obtained	
No previous schooling	1 (<1%)
Elementary school	55 (6%)
Middle school	86 (9%)
High school	210 (21%)
College	133 (13%)
University	406 (41%)
Above graduate school	96 (10%)
Residency	
Dormitory residence	9 (<1%)
Number of household members sharing main residence	
0	1 (<1%)
1	53 (5%)
2	96 (10%)
3-4	693 (70%)
5-6	129 (13%)
>6	15 (2%)
Number of children <10 years sharing main residence	
0	728 (74%)
1	146 (15%)
2	106 (11%)
3-4	7 (<1%)
Employment status	
Employed/self-employed	634 (64%)
Unemployed	117 (12%)
In school/university	236 (24%)
Medical status	
Concomitant medication	45 (5%)
Current controlled non-serious chronic conditions	56 (6%)
Hypertension	8 (1%)
Hyperlipidaemia	6 (1%)
Dyslipidaemia	4 (<1%)
Hypothyroidism	4 (<1%)
Osteoporosis	4 (<1%)
Previous diagnosed[a] meningococcal disease	13 (1%)

[a]Not confirmed from records/laboratory test.

figure reported in the 2010 census (69%) [16]. Only 9 of the 987 subjects lived in a dormitory residence and nearly three-quarters of subjects did not share their main residences with children under 10 years old. Thirteen subjects reported previous meningococcal disease; diagnosis of meningococcal disease caused by *N. meningitidis* was however not confirmed from (medical) records/ laboratory test results or by the treating clinician and thus may have included cases of viral meningoencephalitis or other forms of non-meningococcal meningitis. Six percent had controlled non-serious chronic conditions (3-4% of subjects in the youngest three age groups, and 10% and 9% of subjects in the >39-49 years and >49-55 years groups, respectively).

The highest percentage of subjects with hSBA titres ≥4 or ≥8 was observed for serogroup W (hSBA titres ≥4: 76% and hSBA titres ≥8: 74%), and the lowest percentage was observed for serogroup A (hSBA titres ≥4: 15% and hSBA titres ≥8: 9%). The percentage of subjects with hSBA titres for serogroups C and Y were similar (Table 2). When the 13 subjects with previous meningococcal disease were excluded from the analysis, GMTs were very similar to those presented for the entire study population (GMTs [and 95% CI] serogroup A: 2.56 [2.45-2.67]; C: 5.14 [4.78-5.53]; W: 22.75 [2-.57-25.16]; Y: 5.25 [4.84-5.69]).

When stratified by age group, observed trends for the prevalence of bactericidal antibodies against serogroups A, C, W were similar to those seen for the entire population. There was some variation among age groups for individual serogroups (Fig. 1A); percentages of subjects with hSBA titres ≥4 and ≥8 and GMTs were highest for the >19-29 years age group, compared with other age groups, except for serogroup C, where the highest GMTs were observed for the >49-55 years group. Similarly, results by region showed the same trend as for the

Table 2. Percentage of subjects 11 to 55 years of age with human serum bactericidal assay (hSBA) titres ≥4 and ≥8, and hSBA geometric mean titres (95% confidence interval), for the entire study population

	Serogroup, % (95% confidence interval)			
	A (N = 986)	C (N = 986)	W (N = 985)	Y (N = 986)
hSBA titres ≥4	15% (12-17%)	48% (45-51%)	76% (73-79%)	44% (40-47%)
hSBA titres ≥8	9% (7-11%)	34% (31-37%)	74% (71-77%)	36% (33-39%)
GMT, μg/mL	2.56 (2.45-2.67)	5.14 (4.78-5.52)	22.63 (20.47-25.01)	5.28 (4.87-5.72)

hSBA, human serum bactericidal assay; GMT, hSBA geometric mean titre.

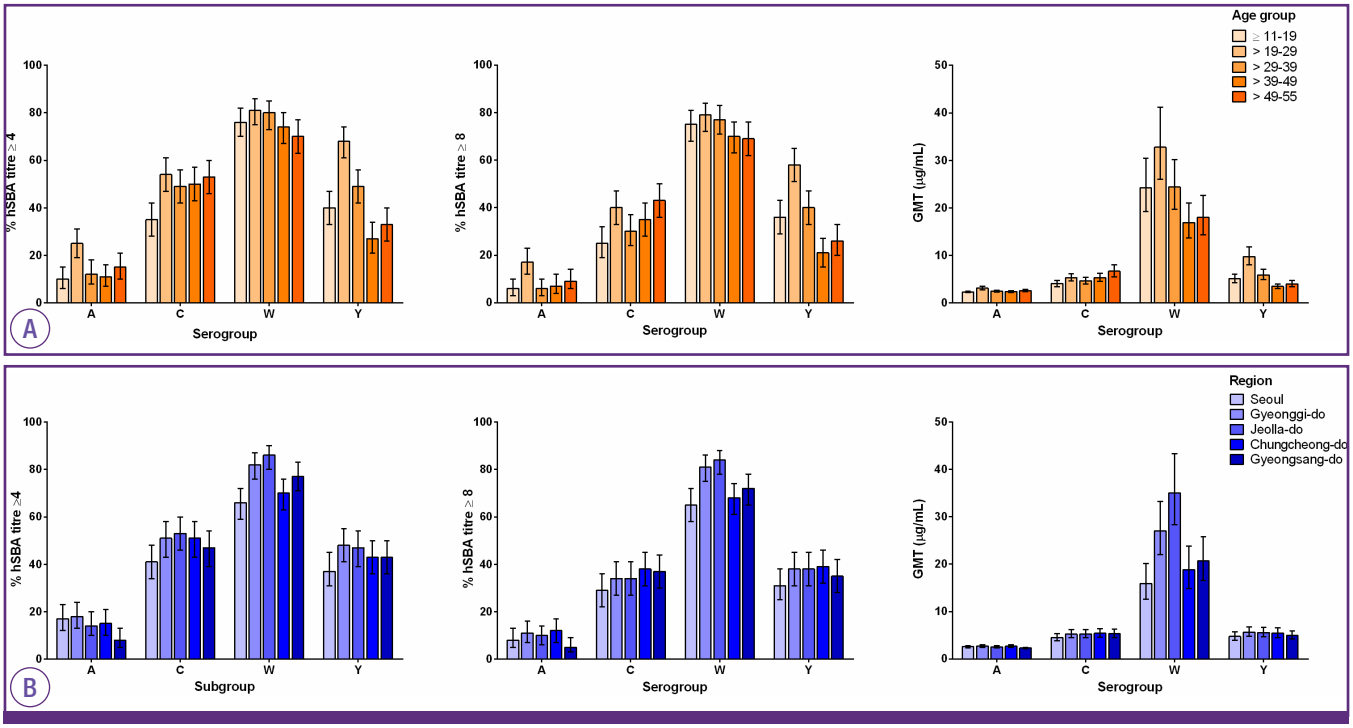

Figure 1. Percentage of subjects 11 to 55 years of age with human serum bactericidal assay (hSBA) titres ≥4, ≥8 and hSBA geometric mean titres (GMTs) for each of the serogroups, stratified by (A) age group and (B) region of Korea.

entire study population, although there were some small regional variations, with higher prevalence of bactericidal antibodies seen in the Jeolla-do region for serogroup W and the lowest prevalence for all serogroups seen in Seoul (Fig. 1B).

Discussion

This is the first sero-epidemiological study on bactericidal antibodies against *N. meningitidis* A, C W and Y serogroups in the Korean population. A high percentage of subjects in this study had hSBA titres ≥4 for serogroup W. An hSBA titre of ≥4 has been previously identified as a surrogate of protection against meningococcal disease [17], which suggests that natural immunity to serogroup W may be prevalent in the Korean population. Percentages of subjects with titres considered protective were similar for serogroups C and Y (approximately half of subjects). The smallest percentage of subjects with titres considered protective was observed for serogroup A. These trends were very similar across regions and age groups.

A previous vaccine trial in adolescents and adults in Korea also showed the same trends as those seen in the current study [14]. However, the observed percentages of subjects with hSBA titres ≥4 and ≥8 and GMTs for serogroups C, W and Y were slightly lower than those observed in the vaccine trial. Prevalence of bactericidal antibodies (subjects with protective titres ≥4 or ≥8) against serogroup A was similar in the two studies. The differences in observations between the two studies may be at least partially influenced by the differences in the included study populations, for example, the mean age of participants was much lower in the vaccine trial (19 years, compared with 34 years in the current study). In the current study, the highest prevalence of bactericidal antibodies was seen in the >19-29 years age group, so the increased proportion of younger subjects in the previous study may have influenced the mean antibody levels detected.

Our study included generally healthy subjects, including those with non-serious chronic conditions. Some differences were observed between the included study population and general statistics for the Korean population, which may impact the generalizability of the results. Additionally, the extrapolation of these results to subjects with serious chronic conditions should be made with caution. Similarly, as this was a small study involving only six sites, extrapolation of the results to the Korean population as a whole should also be made with caution.

High prevalence of bactericidal antibodies against serogroup W has been observed in trials in other countries. Recent vaccine trials in the United States, Costa Rica and Germany also found higher levels of bactericidal antibodies against serogroup W than any of the other three serogroups in non-vaccinated subjects [18-20]. The high prevalence of bactericidal antibodies against serogroup W may be a result of increased carriage in this population, compared with serogroups A, C and Y. Although carriage was not explored in this study, a number of previous studies in Korea have evaluated carriage in different populations. A study by Park and colleagues found that the highest proportion of groupable isolates in Korean army trainees were serogroup W (29.5%) [12]. A separate study on carriage in first year university students found that serogroup C was the most frequent serogroup, in the five out of eight of the groupable isolates [11]. In contrast, in a study of serogroup distribution in young children in Korea, only 6% of cerebrospinal fluid specimens were serogroup C, and none were of serogroup W; the vast majority were of either serogroup X or Y [21]. Despite this variation in study findings, there has been an observed increase in the proportion of cases caused by serogroup W in neighbouring China in the past few years, which may possibly have increased carriage in Korea [22]. Globally, the incidence of cases caused by serogroup W has been increasing since the 2000 Hajj outbreak [23, 24]. In England, MenW cases have increased annually from 22 in 2009 to 117 in 2014. More recently, a steep increase was observed in the number of deaths, from four deaths annually between 2009 and 2012 to 24 deaths between 2013 and 2014, including, for the first time in a decade, deaths in children [25]. One case in Korea in 2013 has also been attributed to serogroup W, although data on cases in general in Korea are limited [26]. Further research on serogroup carriage in this population is needed to fully understand its role in serum bactericidal activity across serogroups. Additionally, although the reasons behind the higher levels of serum bactericidal antibodies against serogroup W (relative to the other three serogroups) are currently unclear, Lee and colleagues discussed the specificity of the antibodies to serogroup W and suggested that the high baseline titres seen in their study were possibly influenced by antibodies which were not specific to serogroup W capsular polysaccharide (e.g. cross-reactive antibodies), which may also be the case in this study [14]. Currently there is no data that suggests that certain population characteristics may explain differences in seropositivity between serogroups, but the available data is limited and may deserve further investigation.

As observed in the current study, studies in other countries

have also reported an age effect on bactericidal antibody prevalence for serogroups A, C, W and Y. As with our study, those in Canada, the UK and Burkina Faso reported a peak in bactericidal antibody prevalence for serogroups A and W in adolescents and young adults (16-29 years) [27-29]. This peak is likely reflective of the higher carriage and incidence of meningococcal disease in this age group [10]. In our study, the highest percentage of subjects with bactericidal antibodies to serogroup C was in the oldest age group, which appears similar to observations from studies in Canada and Turkey, where the highest prevalence in adults was seen in the > 30 years or ≥40 years age brackets, respectively [28, 30].

This study provides insight into the prevalence of bactericidal antibodies against *N. meningitidis* serogroups A, C, W and Y in the generally healthy Korean adolescent and adult population, including those with controlled non-serious chronic conditions. Among *Neisseria meningitidis* serogroups A, C, W and Y, serum bactericidal antibodies were most prevalent against serogroup W and least prevalent against serogroup A, and mirrored those seen in a previous study in Korean adolescents and adults. On average, hSBA titres were highest in young adults (>19-29 years), for three (A, W and Y) out of four of the serogroups. The trends in bactericidal antibodies prevalence across the serogroups were similar across age groups and regions. Whilst the reasons for these differences in prevalence are not completely understood, carriage and non-specificity of antibody to serogroup W capsular polysaccharide may play a role in explaining the high prevalence of bactericidal antibody against serogroup W observed in this study.

Author Contributions

HYS and MH designed the study, J-HK, YM, SYL, JHK, K-YL, SHM, HYS and DSJ conducted the study, YM and MH were involved in data analysis and interpretation. All authors were involved in generation of the manuscript and approved the decision to submit for publication.

Acknowledgements

The authors would like to thank all the administrative, clinical and laboratory staff at the participating centres and all subjects who participated in the study. The authors would also like to extent their particular thanks to the following people for their contribution to the study: Minyoung Lim (study operations), Sonja Haegele (laboratory analysis), Elvira Dijk (data management), Jennifer Howie (editorial assistance in preparing manuscript), Nicholas Roubinis (statistics), Areum Lee, Francesca Dall'Acqua (statistical programming) and John Weil.

Conflicts of Interest

YM, HYS and MH were permanent employees of Novartis group companies (YM: now GSK group companies) at the time of the study. JHK received research funds from Novartis and GSK Korea, honoraria from MSD, Pfizer and Sanofi-Pasteur Korea. DSJ received research funds from Novartis and GSK Korea, and honoraria from MSD and Sanofi-Pasteur Korea. The other authors declare no conflicts of interest.

Funding

This study was funded by Novartis Vaccines and Diagnostics, Inc. (now GlaxoSmithKline LLC)

ORCID

Jin-Han Kang http://orcid.org/0000-0003-1610-6742
Yan Miao http://orcid.org/0000-0002-7728-3112
SooYoung Lee http://orcid.org/0000-0002-5354-3135
Jong-Hyun Kim http://orcid.org/0000-0001-8641-7904
Kyung-Yil Lee http://orcid.org/0000-0001-6510-1580
Sang Hyuk Ma http://orcid.org/0000-0002-4835-9704
Dae Sun Jo http://orcid.org/0000-0002-3141-9539
HyoYoung Song http://orcid.org/0000-0001-7121-7475
Mendel Haag http://orcid.org/0000-0001-7895-7556

References

1. Khatami A, Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. Expert Rev Vaccines 2010;9:285-98.
2. Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, Fermon F, Klugman KP, Ramsay M, Sow S et al. Global epidemiology of invasive meningococcal disease. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013;11:17.
3. Vyse A, Anonychuk A, Jäkel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther 2013;11:597-604.
4. Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, McIntyre P, Ramsay ME, Sáfadi MA. The changing and dynamic epidemiology of meningococcal disease. Vaccine 2012;30 (Suppl 2):B26-36.

5. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine 2009;24 (Suppl 2): B51-63.
6. Vyse A, Wolter JM, Chen J, Ng T, Soriano-Gabarro M. Meningococcal disease in Asia: an under-recognized public health burden. Epidemiol Infect 2011;139;967-85.
7. Kim JH. Infectious diseases in children and adolescents in the Republic of Korea; Past & recent status. Korean J Pediatr 2011;54:489-500.
8. Bae SM, Kang YH. Serological and genetic characterization of meningococcal isolates in Korea. Jpn J Infect Dis 2008;61:434-7.
9. Lee SO. Commencement of the meningococcal vaccination for the republic of Korea army. Infect Chemother 2013;45:113-5.
10. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:853-61.
11. Durey A, Bae SM, Lee HJ, Nah SY, Kim M, Baek JH, Kang YH, Chung MH, Lee JS. Carriage rates and serogroups of Neisseria meningitidis among freshmen in a University dormitory in Korea. Yonsei Med J 2012;53:742-7.
12. Park H, Lee DH, Seo PW, Kim SH, Choi TY, Kim JH. Carrier rate, serogroup and vaccination effect of Neisseria meningitidis on army trainees in Korea. Chungbuk Med J 1995; 5:45-57.
13. Kellerman SE, McCombs K, Ray M, Baughman W, Reeves MW, Popovic T, Rosenstein NE, Farley MM, Blake P, Stephens DS; Georgia Emerging Infections Program. Genotype-specific carriage of Neisseria meningitidis in Georgia counties with hyper- and hyposporadic rates of meningococcal disease. J Infect Dis 2002;186:40-8.
14. Lee HJ, Chung MH, Kim WJ, Hong YJ, Choi KM, Lee J, Oh CE, Welsch JA, Kim KH, Hong KB, Dagnew AF, Bock H, Dull PM, Odrljin T. Immunogenicity and safety of a novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) in healthy Korean adolescents and adults. Int J Infect Dis 2014;28:204-10.
15. Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, Langley JM, McNeil S, Dull PM, Ceddia F, Anemona A, Halperin SA, Dobson S, Pollard AJ. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. JAMA 2008;299:173-84.
16. Korean Statistical Information Service. Statistical database. Available at: http://kosis.kr/eng/statisticsList/statisticsList_01List.jsp?vwcd=MT_ETITLE&parmTabId=M_01_01. Accessed 17 December 2014.
17. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med 1969;129:1307-26.
18. Alberer M, Burchard G, Jelinek T, Reisinger EC, Meyer S, Forleo-Neto E, Dagnew AF, Arora AK. Immunogenicity and safety of concomitant administration of a combined hepatitis A/B vaccine and a quadrivalent meningococcal conjugate vaccine in healthy adults. J Travel Med 2015;22: 105-14.
19. Arguedas A, Soley C, Loaiza C, Rincon G, Guevara S, Perez A, Porras W, Alvarado O, Aguilar L, Abdelnour A, Grunwald U, Bedell L, Anemona A, Dull PM. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. Vaccine 2010; 28:3171-9.
20. Jackson LA, Baxter R, Reisinger K, Karsten A, Shah J, Bedell L, Dull PM; V59P13 Study Group. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis 2009;49:e1-10.
21. Kim SA, Kim DW, Dong BQ, Kim JS, Anh DD, Kilgore PE. An expanded age range for meningococcal meningitis: molecular diagnostic evidence from population-based surveillance in Asia. BMC Infect Dis 2012;12:310.
22. Li J, Li Y, Shao Z, Li L, Yin Z, Ning G, Xu L, Luo H. Prevalence of meningococcal meningitis in China from 2005 to 2010. Vaccine 2015;33:1092-7.
23. Abad R, López EL, Debbag R, Vázquez JA. Serogroup W meningococcal disease: global spread and current affect on the Southern Cone in Latin America. Epidemiol Infect 2014;142:2461-70.
24. Lingappa JR, Al-Rabeah AM, Hajjeh R, Mustafa T, Fatani A, Al-Bassam T, Badukhan A, Turkistani A, Makki S, Al-Hamdan N, Al-Jeffri M, Al Mazrou Y, Perkins BA, Popovic T, Mayer LW, Rosenstein NE. Serogroup W-135 meningococcal disease during the Hajj, 2000. Emerg Infect Dis 2003;9:665-71.
25. Public Health England. Continuing increads in meningococcal group W (MenW) disease in England. Health Protection Report 2015;9. Available at: www.gov.uk/government/uploads/system/uploads/attachment_data/file/407865/hpr0715_men-w.pdf. Accessed 16 March 2015.
26. Sim SH, Heo JY, Kim EC, Choe KW. A case of meningococ-

cal sepsis and meningitis with complement 7 deficiency in a military trainee. Infect Chemother 2013;45:94-8.
27. Trotter CL, Findlow H, Borrow R. Seroprevalence of serum bactericidal antibodies against group W135 and Y meningococci in England in 2009. Clin Vaccine Immunol 2012;19:219-22.
28. Pollard AJ, Ochnio J, Ho M, Callaghan M, Bigham M, Dobsong S. Disease susceptibility to ST11 complex meningococci bearing serogroup C or W135 polysaccharide capsules, North America. Emerg Infect Dis 2004;10:1812-5.
29. Trotter CL, Yaro S, Njanpop-Lafourcade BM, Drabo A, Kroman SS, Idohou RS, Sanou O, Bowen L, Findlow H, Diagbouga S, Gessner BD, Borrow R, Mueller JE. Seroprevalence of bactericidal, specific IgG antibodies and incidence of meningitis due to group A Neisseria meningitidis by age in Burkina Faso 2008. PloS one 2013;8:e55486.
30. Ceyhan M, Yildirim I, Balmer P, Riley C, Laher G, Andrews N, Borrow R, Kurt N, Turgut M, Aydogan A, Ecevit C, Uysal G, Schultze V. Age-specific seroprevalence of serogroup C meningococcal serum bactericidal antibody activity and serogroup A, C, W135 and Y-specific IgG concentrations in the Turkish population during 2005. Vaccine 2007;25:7233-7.