HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 4, 1051–1055
http://dx.doi.org/10.1080/21645515.2015.1108502

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REVIEW

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Impact of vaccination on meningococcal epidemiology

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ABSTRACT

Neisseria meningitidis may cause invasive disease (meningitis and sepsis), leading to considerable disease burden and mortality. However, effective vaccines are available against most pathogenic serogroups. Large-scale vaccination campaigns with the MCC vaccine conducted in UK and with MenAfriVac in the Sahel have clearly demonstrated the direct and indirect effect of immunization programmes on disease and carriage. Moreover, the introduction of novel subcapsular vaccines against serogroup B, which may cross-protect against other serogroups, is likely to have a further effect on trends. Accurate data collection is key to elaborate vaccination strategies able to reduce meningococcal disease burden through direct protection and herd immunity.

ARTICLE HISTORY
Received 30 September 2015
Accepted 11 October 2015

KEYWORDS
epidemiology; invasive meningococcal disease; meningococcus; *Neisseria meningitidis*; vaccination

Neisseria meningitidis (meningococcus) is a member of the bacterial family *Neisseriaceae*. Meningococci are a common bacterial commensals of the nasopharynx, but also important exclusive human pathogens, which may cause devastating invasive diseases (IMD), such as meningitis and sepsis. There are 13 serogroups of *N. meningitidis* characterized by different capsular polysaccharides; only 6 of them (A, B, C, W, X, and Y) cause most life-threatening invasive disease.[1] The pathogenic strains belong to few genetically defined clonal complexes that may emerge and spread worldwide.[2,3]

IMD may occur as sporadic cases, outbreaks and epidemic.[4] There are large geographical variation in the incidence of IMD throughout the world: the highest incidence rates are usually observed in the Sahel, from Senegal to Ethiopia (the so-called African meningitis belt).[1]

Because of the dynamic nature of IMD epidemiology, the global distribution of the different serogroups of *N. meningitidis* may change over time.[5] Serogroup A (MenA) has long been a cause of repeated epidemics in sub-Saharan Africa, but outbreaks of MenA also occurred in industrialized countries until World War II, before disappearing for reasons that remain undefined.[1] Serogroup B and C are the common causes of sporadic cases, local clusters, and outbreaks of IMD in the industrialized world. Some strains, belonging to the hypervirulent ST-11 clonal complex of serogroup C, are associated with severe clinical presentation and high lethality during outbreaks.[4] Serogroup Y is also quite common in the western world, being responsible of increasing IMD rates not only in the United States but also in several European countries.[6] Finally, serogroup W, which emerged with outbreaks associated with the Hajj pilgrimage,[7] shows now an increasing trend in England and Wales.[8]

The development and introduction of more effective vaccines against different meningococcal serogroups is influencing the global epidemiology of IMD. Most of the changes in IMD trends are reported after the introduction of vaccines against *N. meningitidis* of serogroup C and serogroup A, which were mostly used in Western countries and in sub-Saharan Africa, respectively. A further impact on the disease burden is expected with the introduction of new vaccines which are effective against other serogroups. Furthermore, at least 2 subcapsular, protein-based, serogroup B meningococcal vaccines, whose use is expected to increase, are likely to provide cross-protection also against other meningococci.[9]

In order to plan innovative strategies with currently available and novel vaccines, it is important to quantify the impact of ongoing vaccination, disentangling the effect on disease and carriage.

Meningococcal dynamics: Carriage vs. disease

To interpret the impact of vaccination strategies on the trend of IMD, a precise knowledge of the dynamic of meningococcal infection is required. In particular, carriage rates and the disease-to-carriage ratio are important parameters in order i) to understand how meningococcus circulates in human populations, ii) to evaluate changes in trends and the main drivers of IMD outbreaks, and iii) to quantify the potential impact of vaccination as the result of direct and indirect effects.

It is well known that asymptomatic carriage of *N. meningitidis* is common while invasive disease is a rare outcome.[10] Carriage plays an important role in the transmission and spread of bacterial infection, but *N. meningitidis* carriage strains are somewhat different, from those involved in IMD, and only a subset of them (known as hyperinvasive lineages) causes disease. Asymptomatic infection with pathogenic and non-pathogenic *Neisseriae*, including *Neisseria lactamica*, may contribute

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to the development of protection, through the generation of natural immunity against disease, as already reported.[12] To this purpose, repeated episodes of meningococcal and *Neisseria lactamica* carriage are likely to occur through a lifetime.[10-12] However, to what extent cross-protection, which is likely to be short-lived, reduces the risk of infection and/or disease remains undefined.[11]

The force of infection, carriage prevalence, and the risk of meningococcal disease given infection clearly vary with age, geographical area, and serogroup. The population prevalence of meningococcal carriage may be as high as 10%, reaching a peak among teenagers.[13] Thus, the peak of IMD observed in teenagers is probably due to increased transmission or to other factors, such as passive smoking.

Several serogroups are limited to a specific geographical context (which is a proxy for behavioral and environmental factors), determining an interaction between the effects of the 2 variables (namely, geographical area and serogroup). Paradigmatic examples are represented by the endemic/epidemic dynamics of 2 vaccine preventable serogroups, such as A and C, which predominate respectively in the Sahel and in Europe.

Serogroup A carriage dynamics in the african meningitis belt

Serogroup A has long been the most important cause of meningitis in the African belt, where the epidemiological pattern of meningococcal disease is characterized by hyperendemicity during the dry season alternating with endemic incidence during the rainy season. Epidemics may also occur, usually during the second half of the dry season, in cycles of 7 to 10 y.[14] Until the introduction of a meningococcal serogroup A conjugate vaccine (MenAfriVac),[15] most of the epidemics were due to MenA, but serogroup C, and, more recently (since the year 2000), W, and X, have also caused epidemics. Compared with Europe, young children and younger adults have a higher risk of being carriers. Carriage of pathogenic serogroups appears to be significantly higher among close contact belonging to the immediate family group compared with all the other household contacts, and a higher rate has been found among individuals sleeping in the same room with individuals affected by IMD as compared with other household members.[16] The shift from endemic to seasonal hyper-endemic appears to be related to an increased risk of meningitis given colonization, as suggested by higher case-carrier ratios, whereas epidemics are likely to be caused by a substantial increase in transmission and colonization.[14,17]

Serogroup C carriage dynamics in industrialized countries

Serogroup C carriage is rare compared with the other serogroups,[10,18] but the results of studies conducted in different settings are not consistent, some of them showing low rates of carriage during outbreaks of MenC disease, while others have found relatively high rates.[19] The risk of invasive disease is likely to be higher with serogroup C hypervirulent strains, which are probably more transmissible, with a short duration of carriage leading to a low prevalence and to a higher risk of death.[20,21] With these strains, most cases of meningitis occur within few days after the meningococcal infection.[11,22] Overall, these factors may explain the rapid dynamic of MenC infection, in particular that of strains belonging to the ST-11 clonal complex,[5] which is characterized by higher IMD risk and low prevalence of carriage.

Impact of vaccination: population effect and vaccines effectiveness

None of the meningococcal conjugate vaccines has been tested in randomized controlled trials with disease end-points; in fact, they are not justified in presence of immunological correlates of protection that provide a reliable measures of vaccine efficacy.[23] Therefore, the efficacy against IMD may be estimated from post-licensure studies of population effect and vaccine effectiveness.[24]

Impact of vaccination against MenC on IMD and carriage in industrialized countries

Variability in the incidence of IMD in the absence of vaccination, both overall and by serogroup, complicates the assessment of vaccine effects.[24] The United Kingdom was the first country to introduce a national immunization program with the MCC vaccine at the end of 1999, offering the vaccine to all adolescents between 15 and 17 y of age. Infants were also routinely immunized.[25] Serogroup C IMD cases almost disappeared after large-scale vaccination campaigns with MCC vaccine, with a reduction of more than 98% in target age groups and of more than 90% in unvaccinated age groups, providing evidence of the strong effect of the vaccine.[26] In particular, an overall reduction of 86.7% was observed for the target age groups in 2001 compared with 1999;[27] by 2001/2002, the number of IMD cases due to MenC was 89–94% lower than in 1998/1999 in each age group under 20 years,[26] and by 2007–2008 a decrease of over 97% compared to 1998–1999.[28]

However, the results of long-term studies were disappointing, showing that the protection induced by the MCC vaccine may fall to low levels after one year in children vaccinated in the first months of age,[29] requiring a booster at one year of age.[28] Thus, catch-up campaigns were conducted in order to obtain herd protection, generated by immunizing teenagers, which are those that amplify *Neisseria* circulation through asymptomatic transmission.[30]

In the Netherlands, MenC IMD significantly decreased among vaccinated persons, and a sharp decline was observed also in unvaccinated cohorts after routine administration of a single dose of vaccine at 14 months and a catch-up campaign for children and adolescents from 1 to 18 y of age generating herd protection for infants.[31,32] In Spain, where vaccination coverage among adolescents was suboptimal, the outcome of immunizations campaigns was not as good as expected in terms of herd protection.[33]

Vaccine effectiveness ranged from 75% in Australia, after a single dose at 12 months and catch-up vaccination for those aged under 20 years, to 96.8% in Canada, where 82.1% of those aged 2 months to 20 y were vaccinated.[34] Declines in incidence rates of IMD were observed in other countries, from Canada, to Italy, and Brazil.[35-37]

MCC vaccines appear to provide high levels of protection in the short term[20,38] and reduce the prevalence of serogroup carriage, resulting in herd immunity;[18,39] however, the duration of

the protection is age-dependent, being longer in older children compared with infants.[40]

While the polysaccharide vaccine had no effect on MenC carriage, this can be instead prevented or reduced by the use of the conjugate vaccine.[19] In fact, large-scale carriage studies have shown that MCC vaccine have an impact on the asymptomatic carriage.[18] Studies conducted in UK in 1999 (year of MCC vaccine introduction), in 2000 and 2001, showed a significant decrease in the prevalence of serogroup C carriage among 15 to 19 y old students. The percentage of MenC of all the isolates declined from 2.51 in 1999 to 0.48% in 2001 (rate ratio: 0.19); in the 2001 survey, 0.40% of the unvaccinated carried MenC compared with 1.61% of the unvaccinated individuals. Vaccine effectiveness against carriage was 75%, with a disproportionate impact on the carriage of sequence type (ST)-11 complex serogroup C meningococci (rate ratio: 0.06). The impact of MCC vaccine on this population was consistent with herd immunity. Remarkably, the reduction in serogroup C carriage lasted at least 2 years, with no evidence of serogroup replacement,[30] as confirmed by further studies.[41] This is consisted also with the results of studies showing an increase in the prevalence of protective SBA (serum bactericidal activity) titers in the post-vaccination era when compared with pre-vaccination findings.[42]

Overall, the results of vaccine impact studies show that MCC vaccine may reduce MenC carriage. To this purpose, adolescents have both the highest rates of transmission and carriage; thus, they are likely to sustain meningococcal circulation in the population. Mathematical models suggest that the elimination of the serogroup C meningococcal disease depends on the degree and the duration of protection conferred by vaccination[10] and that the introduction of a booster dose in adolescents may have both an individual and herd immunity effect. For this reason, teenagers are now considered the main target for large catch-up campaigns.[10]

Impact of vaccination campaigns in the African meningitis belt

Successful vaccination campaigns have been also conducted in the African meningitis belt. In 2000, the World Health Organization launched the idea to make a safe and effective vaccine specifically for Africa at an African price. A public-private partnership funded by the Bill & Melissa Gates Foundation started the project leading to the production of MenAfriVac, a conjugated MenA vaccine.[43] Starting from 2010, the vaccine coverage for MenA vaccine in Burkina Faso was estimated at >90%;[44-47] No cases were identified the next year. Similar results were obtained in Chad in 2011/13.[46,47] In 3 regions where mass-vaccination was implemented in 2011, the incidence of IMD in 2012 was 2.5 per 100,000 (with no case of MenA IMD) vs. 43.8 per 100,000 in the rest of the country, with a 94% difference in crude incidence and an incidence rate ratio of 0.096. Moreover, serogroup A carriage declined significantly from the pre- to post-vaccination period (adjusted odds ratio: 0.019).[46] The GAVI is now supporting the introduction of the vaccination, which seems to be active also against MenA carriage, in several African countries. Unfortunately, other *N. meningitidis* serogroups are devastating the African meningitis belt. As mentioned above, an epidemic of MenC caused about 8,000 cases and more than 500 deaths in Niger between January and May 2015. The epidemic was worrying and to some extent unprecedented, because it was due to a strain which is not usually found in sub-Saharan Africa, and the appropriate vaccine was in short supply.[48] To this regard, it should be mentioned that, over the past 40 years, serogroup C has caused only sporadic cases and a few localized outbreaks in Africa, generally co-circulating with serogroup. These outbreaks occurred in Nigeria in 1975, in Niger in 1991, and in Nigeria in 2013–2014 (http://www.who.int/mediacentre/news/situation-assessments/meningitis-niger/en/). Thus, the recent MenC outbreak occurred in Niger appears to open new scenarios, launching a further challenge to overwhelmed health systems in poor-resource countries.

Conclusions

The inclusion of the MCC vaccine in the infant schedule, with a consequent reduction in *N. meningitidis* serogroup C disease, is a positive example of the impact of vaccination on meningococcal epidemiology, promoting the introduction of novel vaccines against other meningococcal serogroups.[49] Nevertheless, the rapid loss of protection conferred by the vaccine, when administered in the early phase of life, suggests that a later booster may be necessary to maintain herd protection in the population, ensuring the success of immunization programmes. The result of large-scale vaccination campaigns based on the MenAfriVac in the Africa meningitis belt is encouraging, strengthening the need for preparedness plans against different meningococcal serogroups such as C and W.

At last, innovative vaccines, such as the novel sub-capsular vaccine against meningococcus B, are being introduced in several countries. However, there are still gaps in knowledge which concern the duration of the protection, the impact of the vaccine on nasopharyngeal carriage dynamic and, consequently, on herd protection. The possibility of cross-protection conferred by MenB vaccine antigens against other serogroups need also to be further assessed.

Finally, any vaccination policy should be carefully evaluated by monitoring the impact on IMD, carriage, and possible capsule replacement.

Abbreviations

GAVI	The Global Alliance for Vaccine and Immunization
IMD	invasive meningococcal disease
MCC	meningococcal C conjugate vaccine
MenA	meningococcus of serogroup A
MenAfriVac	meningococcal A conjugate vaccine developed for Africa
MenC	meningococcus of serogroup C
SBA	serum bactericidal activity
ST	Sequence Type

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Stephen DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitides*. Lancet 2007; 369:2196-210; PMID:17604802; http://dx.doi.org/10.1016/S0140-6736(07)61016-2

[2] Urwin R, Maiden MCJ. Multi-locus sequence typing: a tool for global epidemiology. Trends Microbiol 2003; 11:479-487; PMID:14557031; http://dx.doi.org/10.1016/j.tim.2003.08.006

[3] Turner KME, Feil EJ. The secret life of the multilocus sequence type. Int J Antimicrob Agents 2007; 29:129-35; PMID:17204401; http://dx.doi.org/10.1016/j.ijantimicag.2006.11.002

[4] Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine 2009 Jun 24; 27 Suppl 2:B51-63

[5] 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; PMID:22178525; http://dx.doi.org/10.1016/j.vaccine.2011.12.032

[6] Bröker M, Emonet S, Fazio C, Jacobsson S, Koliou M, Kuusi M, Pace D, Paragi M, Pysik A, Simões MJ, Skoczynska A, Stefanelli P, Toropainen M, Taha MK, Tzanakaki G. Meningococcal serogroup Y disease in Europe: Continuation of high importance in some European regions in 2013. Hum Vaccin Immunother 2015; 11(9):2281-6; PMID:26036710; http://dx.doi.org/10.1080/21645515.2015.1051276

[7] Taha MK, Achtman M, Alonso JM, Greenwood B, Ramsay M, Fox A, Gray S, Kaczmarski E. Serogroup W135 meningococcal disease in Hajj pilgrims. Lancet 2000; 356 (2000):p. 2159; PMID:11191548

[8] Ladhani S, Beebeejaun K, Lucidarme J, Cambell H, Gray S, Kaczmarski E, Ramsay M, Borrow R. Increase in endemic *Neisseria meningitidis* capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis 2015; 60:578-85; PMID:25389259; http://dx.doi.org/10.1093/cid/ciu881

[9] Hong E, Giuliani MM, Deghmane AE, Comanducci M, Brunelli B, Dull P, Pizza M, Taha MK. Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control *Neisseria meningitidis* capsular group X outbreaks in Africa? Vaccine 2013 Feb 4; 31 (7):1113-6; http://dx.doi.org/10.1016/j.vaccine.2012.12.022

[10] Trotter CL, Gay NJ, Edmunds WJ. Dynamic models of meningococcal carriage, and the impact of serogroup C conjugate vaccination. Am J Epidemiol 2005; 162:89-100; PMID:15961591; http://dx.doi.org/10.1093/aje/kwi160

[11] Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease. Epidemiol Infect 2006; 134:556-66; PMID:16238823; http://dx.doi.org/10.1017/S0950268805005339

[12] Pollard AJ, Frasch C. Development of natural immunity to *Neisseria meningitidis*. Vaccine 2001; 19:1327-48; PMID:11163654; http://dx.doi.org/10.1016/S0264-410X(00)00333-9

[13] Cartwright K. Meningococcal carriage and disease. In: Cartwright K, ed. Meningococcal disease. Chichester, United Kingdom: John Wiley and Sons, 1995: 115-146.

[14] Koutangni T, Mainassara HB, Mueller JE. Incidence, carriage and case-carrier ratios for meningococcal meningitis in the African meningitis belt: a systematic review and meta-analysis. PLoS One 2015 feb 6 10(2):e0116725; http://dx.doi.org/10.1371/journal.pone.0116725

[15] MenAfriCar consortium. The Diversity of Meningococcal Carriage Across the African Meningitis Belt and the Impact of Vaccination With a Group A Meningococcal Conjugate Vaccine. J Infect Dis. 2015 Oct 15; 212(8):1298-307; http://dx.doi.org/10.1093/infdis/jiv211

[16] Trotter CL, Greenwood BM. Meningococcal carriage in the African meningitis belt. Lancet Infect Dis 2007; 7:797-803; PMID:18045562; http://dx.doi.org/10.1016/S1473-3099(07)70288-8

[17] Mueller JE, Gessner BD. A hypothetical explanatory model for meningococcal meningitis in the African meningitis belt. Int J Infect Dis 2010; 14:e553-559; PMID:20018546; http://dx.doi.org/10.1016/j.ijid.2009.08.013

[18] Maiden MC, Stuart JM: UK meningococcal carriage group. Carriage of serogroup C meningococcal C conjugate polysaccharide vaccination. Lancet 2002; 359:1829-31; PMID:12044380; http://dx.doi.org/10.1016/S0140-6736(02)08679-8

[19] Sàfadi MA, Carvalhanas TR, De Lemos AP, Gorla MC, Salgado M, Fukasawa LO, Gonçalves MG, Higa F, Brandileone MC, Sacchi CT, et al. Carriage rate and effects of vaccination after outbreaks of serogroup C meningococcal disease, Brazil, 2010. Emerg Infect Dis 2014; 20:806-11; http://dx.doi.org/10.3201/eid2005.130948

[20] Trotter CL, Ramsay ME, Kaczmarski EB. Meningococcal serogroup C vaccination in England and Wales: coverage and initial impact of the campaign. Commun Dis Public Health 2002; 5:220-5; PMID:12434692

[21] Trotter CL, Fox AJ, Ramsay ME, Sadler F, Gray SJ, Mallard R, Kaczmarski EB. Fatal outcome from meningococcal disease – an association with meningococcal phenotype but not with reduced susceptibility to benzylpenicillin. J Med Microbiol 2002; 51:855-60; PMID:12435065; http://dx.doi.org/10.1099/0022-1317-51-10-855

[22] Gilmore A, Jones G, Barker M, Soltanpoor N, Stuart JM. Meningococcal disease at the University of Southampton: outbreak investigation. Epidemiol Infect 1999; 123:185-92; PMID:10579436; http://dx.doi.org/10.1017/S0950268899002794

[23] Khatami A, Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. Expert Rev Vaccines 2010; 9:285-98; PMID:20218857; http://dx.doi.org/10.1586/erv.10.3

[24] McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet 2012; 380:1703-11; PMID:23141619; http://dx.doi.org/10.1016/S0140-6736(12)61187-8

[25] Vipond C, Care R, Feavers IM. History of meningococcal vaccines and their serological correlates of protection. Vaccine 2012; 30 (5): Suppl:B10-7; PMID:22607894; http://dx.doi.org/10.1016/j.vaccine.2011.12.060

[26] Campbell H, Borrow R, Salisbury D, Miller E. Meningococcal C conjugate vaccine: the experience in England and Wales. Vaccine 2009; 27 (suppl 2): B20-9; PMID:19477053; http://dx.doi.org/10.1016/j.vaccine.2009.04.067

[27] Balmer P, Borrow R, Miller E. Impact of meningococcal C conjugate vaccine in UK. J Med Microbiol 2002; 51:717-22; PMID:12358061; http://dx.doi.org/10.1099/0022-1317-51-9-717

[28] Borrow R, Abad R, Trotter C, van der Klis FRM, Vazquez JA. Effectiveness of meningococcal serogroup C vaccine programmes. Vaccine 2013; 4477-86; PMID:23933336; http://dx.doi.org/10.1016/j.vaccine.2013.07.083

[29] Trotter CL, Andrews NJ, Kaczmarski, EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogoup C conjugate vaccine 4 years after immunization. Lancet 2004; 364:365-7; PMID:15276396; http://dx.doi.org/10.1016/S0140-6736(04)16725-1

[30] Maiden MCJ, Ibarz-Pav∫n AB, Urwin R, Gray SJ, Andrews NJ, Clarke SC, Walker AM, Evans MR, Kroll JS, Neal KR, et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. J Infect Dis 2008; 197:737-43; PMID:18271745; http://dx.doi.org/10.1086/527401

[31] De Greef SC, de Melker HE, Spanjaard L, Schouls LM, van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. Pediatr Infect Dis 2006; 25:79-80; http://dx.doi.org/10.1097/01.inf.0000195594.41449.c6

[32] Kaaijk P, van der Ende A, Berbers G, van den Dobbelsteen GP, Rots NY. Is a single dose of meningococcal serogroup C sufficient for protection? Experience from the Netherlands. BMC Infect Dis 2012; 12:35; PMID:22316426; http://dx.doi.org/10.1186/1471-2334-12-35

[33] Larrauri A, Cano R, Garcia M, Mateo S. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. Vaccine 2005; 23:4097-100; PMID:15908059; http://dx.doi.org/10.1016/j.vaccine.2005.03.045

[34] De Wals P, Deceuninck G, Boulianne N, de Serres G. Effectiveness of a mass immunization campaign using serogroup C meningococcal conjugate vaccine. JAMA 2004; 292:2491-4; PMID:15562128; http://dx.doi.org/10.1001/jama.292.20.2491

[35] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R; Canadian Immunization Monitoring Program, Active (IMPACT). The impact of childhood meningococcal serogroup C conjugate vaccine program in Canada. Pediatr Infec Dis 2009; 28:220-4; http://dx.doi.org/10.1097/INF.0b013e31819040e7

[36] de Waure C, Miglietta A, Nedovic D, Mereu G, Ricciardi W. Reduction in *Neisseria meningitidis* infection in Italy after Meningococcal C conjugate vaccine introduction: a time trend analysis of 1994-2012 series. Hum Vaccin Immunother 2015 Aug 26; http://dx.doi.org/10.1080/21645515.2015.1078951

[37] de Cantuaria Tauil M, de Carvalho CSR, Vieira AC, Waldman EA. Meningococcal disease before and after the introduction of meningococcal serogroup C conjugate vaccine. Federal District, Brazil. Braz J Infect Dis 2014; 18:379-86; PMID:24698710; http://dx.doi.org/10.1016/j.bjid.2013.11.012

[38] Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001; 357:195-6; PMID:11213098; http://dx.doi.org/10.1016/S0140-6736(00)03594-7

[39] Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England. BMJ 2003; 326:365-6; PMID:12586669; http://dx.doi.org/10.1136/bmj.326.7385.365

[40] Ramsay ME, Andrews N, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccines four years after introduction. Lancet 2004; 364:365-7; PMID:15276396; http://dx.doi.org/10.1016/S0140-6736(04)16725-1

[41] Ibarz-Pav∫n AB, MacLennan J, Andrews NJ, Gray SJ, Urwin R, Clarke SC, Walker AM, Evans MR, Kroll JS, Neal KR, et al. Changes in serogroup and genotype prevalence among carried meningococci in United Kingdom during vaccine implementation. J Infect Dis 2011; 204:1046-53; http://dx.doi.org/10.1093/infdis/jir466

[42] Trotter CL, Borrow R, Findlow J, Holland A, Frankland S, Andrews NJ, Miller E. Seroprevalence of antibodies against serogroup C meningococci in England in the postvaccination era. Clin Vacc Immunol 2008; 15:1694-8; http://dx.doi.org/10.1128/CVI.00279-08

[43] Kupferschmidt K. A new vaccine vanquishes meningitis A in Africa. Science 2014; 345:1265; PMID:25214605; http://dx.doi.org/10.1126/science.345.6202.1265

[44] Centers for Disease Control and Prevention. Serogroup A meningococcal conjugate vaccine coverage after the first national mass immunization campaign-Burkina Faso, 2011. MMWR Morb Mortal Wkly Rep 2012; 61:1022-4; PMID:23254256

[45] Meyer SA, Kambou JL, Cohn A, Goodson JL, Flannery B, Medah I, Messonnier N, Novak R, Diomande F, Djingarey MH, Clark TA, Yameogo I, Fall A, Wannemuehler K. Serogroup A meningococcal conjugate (PsA-TT) vaccine coverage and measles vaccine coverage in Burkina Faso–implications for introduction of PsA-TT into the Expanded Programme on Immunization. Vaccine. 2015; 33:1492-8; PMID:25636915; http://dx.doi.org/10.1016/j.vaccine.2015.01.043

[46] Daugla DM, Gami JP, Gamougam K, Naibei N, Mbainadji L, Narbé M, Toralta J, Kodbesse B, Ngadoua C, Coldiron ME, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. Lancet 2013; 383:40-7; PMID:24035220; http://dx.doi.org/10.1016/S0140-6736(13)61612-8

[47] Gamougam K, Daugla DM, Toralta J, Ngadoua C, Fermon F, Page AL, Djingarey MH, Caugant DA, Manigart O, Trotter CL, et al. Continuing effectiveness of serogroup A meningococcal conjugate vaccine, Chad, 2013. Em Infect Dis 2015; 21:115-8; http://dx.doi.org/10.3201/eid2101.140256

[48] Maurice J. Vaccine shortage threatens spread of meningitis in Niger. Lancet 2015; 385:2241; PMID:26088485; http://dx.doi.org/10.1016/S0140-6736(15)61050-9

[49] Maiden MCJ, MacLennan JM. Fifteen years of protection by meningococcal C conjugate vaccines: lessons from disease surveillance. Clin Infect Dis 2014; 59:1222-4; PMID:25069870; http://dx.doi.org/10.1093/cid/ciu599