http://ijhpm.com
Int J Health Policy Manag 2015, 4(11), 757–761

doi 10.15171/ijhpm.2015.168

IJHPM International Journal of Health Policy and Management

Policy Brief

Need for Optimisation of Immunisation Strategies Targeting Invasive Meningococcal Disease in the Netherlands

Josefien Cornelie Minthe Bousema*, Joost Ruitenberg

Abstract

Invasive meningococcal disease (IMD) is a severe bacterial infectious disease with high mortality and morbidity rates worldwide. In recent years, industrialised countries have implemented vaccines targeting IMD in their National Immunisation Programmes (NIPs). In 2002, the Netherlands successfully implemented a single dose of meningococcal serogroup C conjugate vaccine at the age of 14 months and performed a single catch-up for children ≤18 years of age. Since then the disease disappeared in vaccinated individuals. Furthermore, herd protection was induced, leading to a significant IMD reduction in non-vaccinated individuals. However, previous studies revealed that the current programmatic immunisation strategy was insufficient to protect the population in the foreseeable future. In addition, vaccines that provide protection against additional serogroups are now available. This paper describes to what extent the current strategy to prevent IMD in the Netherlands is still sufficient, taking into account the burden of disease and the latest scientific knowledge related to IMD and its prevention. In particular, primary MenC immunisation seems not to provide long-term protection, indicating a risk for possible recurrence of the disease. This can be combatted by implementing a MenC or MenACWY adolescent booster vaccine. Additional health benefits can be achieved by replacing the primary MenC by a MenACWY vaccine. By implementation of a recently licensed MenB vaccine for infants in the NIP, the greatest burden of disease would be targeted. This paper shows that optimisation of the immunisation strategy targeting IMD in the Netherlands should be considered and contributes to create awareness concerning prevention optimisation in other countries.

Keywords: Immunisation, Invasive Meningococcal Disease (IMD), National Immunisation Programme (NIP), Prevention, Public Health, Vaccines

Citation: Bousema JCM, Ruitenberg J. Need for optimisation of immunisation strategies targeting invasive meningococcal disease in the Netherlands. *Int J Health Policy Manag.* 2015;4(11):757–761. doi:10.15171/ijhpm.2015.168

Article History:
Received: 27 August 2015
Accepted: 11 September 2015
ePublished: 13 September 2015

***Correspondence to:**
Josefien Cornelie Minthe Bousema
Email: josefienbousema@gmail.com

Invasive meningococcal disease (IMD) is a global health threat and has been a cause for serious concern for a number of years. This severe bacterial infectious disease, causing meningitis and sepsis, is caused by the bacterium *Neisseria meningitidis*, or the meningococcus, and has humans as its only reservoir. Over 90% of the cases are caused by 6 serogroups: A, B, C, Y, W, and X.[1] In industrialised countries, including the Netherlands, serogroups B (MenB), C (MenC) and Y (MenY) have mainly had the highest prevalence and caused major outbreaks and hyperendemic diseases since the 1970s.[2,3] Ten percent of the healthy people are asymptomatic carriers of the bacterium and contribute to transmitting the disease.

Worldwide, IMD is associated with a high incidence. Annually, approximately 1.2 million cases are recorded worldwide; of which 7000 occur in Europe.[4] Despite advances in antibiotic therapy and medical treatment, the mortality of IMD is 10% and death can occur within hours or days. Survivors of IMD have a 30% risk of serious long-term complications, such as hearing loss, skin scarring, brain damage, kidney failure, learning disabilities and other neurological abnormalities or limb amputations.[5,6] The disease mainly affects infants and children (immature immune systems), but shows also increased rates among adolescents (highest carriage rates) and elderly (immunosenescence).[6]

Immunisation is considered the best strategy to prime and boost the immune system and prevent individuals from serious, life-threatening IMD.[7] In addition, immunisation reduces the use of antibiotics and therewith the chance to develop antibiotic resistance of meningococci.[8,9] The first meningococcal polysaccharide vaccine was approved in 1978. Since then, in industrialised countries, polysaccharide vaccines have been used to help prevent IMD in high-risk individuals (eg, asplenics) and travellers. Subsequently, despite notable differences between Europe and the United States/Canada in both epidemiology and vaccination strategy, since the beginning of the twentieth century, conjugated monovalent MenC and quadrivalent MenACWY vaccines have been introduced in National Immunisation Programmes (NIPs) of industrialised countries. In addition, one-off catch-ups to immunise adolescents lead to herd protection, as they are the group that carry meningococci. This significantly reduced the incidence and threat of this devastating disease, helped reduce healthcare costs to both patients and healthcare systems, and reduced profound neuropsychological consequences for the affected individuals and their families.[6,10]

A central issue in public health management is the validity of NIPs targeting IMD. In particular, current NIPs seem

Athena Institute, Faculty of Earth and Life Sciences, VU University, Amsterdam, The Netherlands

to insufficiently protect in the near future due to waning antibody levels after primary MenC immunisation.[11] Furthermore, recently 2 vaccines targeting MenB IMD became available: 4CMenB (Bexsero®, GlaxoSmithKline) and LP2086 (Trumenba®, Pfizer) of which only 4CMenB is currently licensed in the European Union (EU). Also, in several countries increases in incidence are seen among MenY IMD and MenW IMD.[8,12,13] As vaccines are available providing protection against these additional serogroups and meningococcal vaccines are also indicated for use in adolescents, alternative immunisation programmes should be considered. Despite these developments, only a limited number of countries updated their NIP. To illustrate, the Netherlands currently uses the same IMD immunisation strategy as was implemented in 2002. Therefore, in order to optimally protect individuals and the society against IMD, this paper validates the strength of the current preventive measures around IMD and examines the need for prevention optimisation and formulates recommendations to optimise the immunisation strategy, using the Netherlands as an example.

Change of Epidemiology in the Netherlands

After the dramatic outbreak of MenC IMD at the beginning of the twentieth century,[14] in 2002, the Netherlands introduced a MenC vaccine in the NIP for children 14 months of age and performed a single catch-up for children ≤18 years of age to provide direct protection to a large cohort and to induce herd immunity.[15] It has been demonstrated that since the last decade, the incidence of all cases of IMD in the Netherlands has markedly declined: 717 cases were reported in 2001 and 111 in 2013.[14,16] The introduction of the MenC vaccine in particular, and the natural decline of incidence of MenB are contributing factors. In 2013, there were 6 cases of MenC IMD, of which all were not vaccinated because of age or nationality, and there were 88 cases of MenB IMD was 88, of which the greatest burden was seen in infants and children. There were 7 and 14 cases of respectively MenW and MenY IMD in 2013, and have, during recent years, slightly increased, particularly in adolescents. These trends are seen in most industrialised countries.[8,12,13] Maintenance of enhanced surveillance results in a better understanding of the changing nature of the epidemiology,[7,16] and detects possible outbreaks and losses in direct protection and herd protection.[17] This is crucial for identifying extended optimal immunisation policies.

Evolving Immunisation Strategies

Introduction of a MenC Adolescent Booster Vaccine to Tackle Waning Antibody Levels

An additional MenC booster dose could be considered to induce long-term protection against MenC IMD. While the MenC immunisation in the Netherlands was successful in decreasing the incidence of MenC IMD (277 cases in 2001 and 6 in 2013),[18] it fails to induce persistent protection.[11,16,19] In particular, waning of antibody levels has been observed after primary immunisation of infants, which in turn is likely to result in a decline in herd protection.[11,19-21] When MenC IMD returns into the population, especially adolescents seem to be at increased risk, as their antibody levels will have declined and they have the highest carriage rates increasing the transmission potential of the bacterium.[11,20] These findings suggest that in the near future a potentially extensive group might be at risk of MenC IMD. Therefore, it is suggested that prevention against MenC IMD needs further optimisation. To tackle this waning immunity, implementation of an adolescent booster seems to evoke higher antibody levels, and long-term and possible lifelong protection.[16] A Dutch study showed that administering a booster dose 9, 12, or 15 years after primary immunisation develops high protective antibody levels that are still at a sufficient level after one year.[19] Furthermore, these results suggest that persisting individual protection increases with the age at which the booster is administered.[19]

As illustrated in Table, recently, Canada, Spain, Ireland, Switzerland, and the United Kingdom introduced a MenC adolescent booster in their NIP to provide long-term protection.[22-25] Furthermore, discussions are being held about the possible use of a MenC vaccine at the moment

Table. Vaccines Targeting IMD Recommended to Healthy People in NIPs (August 2015)

Country	Serogroup	Age
Americas		
Canada	C	2 + 12 mon (2 doses)/12 mon (1 dose); 5-11 y (catch-up[a])
	C or ACWY	12(-24) y (booster)
	B	>2 mon
US	ACWY	11-12 y (1 dose); 16 y (booster)
Europe		
Austria	C or ACWY	12-14 mon (1 dose) – not funded
	ACWY	11-13 y (booster)
Belgium	C	13-18 mon (1 dose)
Cyprus	C	12-13 mon (1 dose)
France	C	12-23 mon (1 dose); 2-24 y (catch-up[a])
Germany	C	11-23 mon; 2-24 y (catch-up[a])
Greece	C	2 + 4 + 6 mon - 5 y (3 doses)
	ACWY	11 y (booster)
Iceland	C	6 + 8 mon (2 doses)
Ireland	C	4 + 13 mon (2 doses); 12-13 y (booster)
Italy	C	13-15 mon (1 dose); 11-18 y (catch-up[a])
Liechtenstein	C	12-15 mon; 11-15 y (catch-up[a])
Luxembourg	C	13 mon (1 dose)
The Netherlands	C	14 mon (1 dose)
Poland	C	2-6 mon (first doses); 8 mon - 19 y (Second dose) – not funded
Portugal	C	12 mon (1 dose)
Spain	C	2 + 12 mon (2 doses); 12 y (booster)
Switzerland	C	12-15 mon (1 dose); 11-15 y (booster)
United Kingdom	C	3 mon (first of 2 doses)
	C & Hib	12-13 mon (Second of 2 doses)
	ACWY	14-15 y (booster) - replaces former C booster
		17-25 y (catch-up[a])
	B	2 + 4 mon (2 doses); 12-13 mon (booster) (from first Sept 2015)

Abbreviations: Hib, *Haemophilus influenzae* type b; IMD, invasive meningococcal disease; NIPs, National Immunisation Programmes. The following European countries have no vaccinations targeting IMD recommended in their NIP: Bulgaria, Croatia, Denmark, Estonia, Finland, Hungary, Latvia, Lithuania, Malta, Norway, Romania, Slovakia, Slovenia, and Sweden.

[a] Catch-up (eg, if previous was dosed missed).

breakthroughs are seen among adolescents/students. These breakthroughs may cause campus-like outbreaks and would result in 'missed opportunities.' To combat the loss of opportunities, the United Kingdom offered, complementary to their MenC adolescent booster, a MenC vaccine to students who enter university for the first time and have not received a dose of MenC over the age of ten years.[26] Moreover, recently, the United Kingdom decided to replace their MenC adolescent booster and student catch-up by a MenACWY vaccine.[26] This will be discussed in the next section. To conclude, due to waning antibody levels after primary immunisation, implementation of a MenC adolescent booster is likely to extend direct protection and herd protection.

Enlarging Protection by Introducing a MenACWY Vaccine

By introduction of a MenACWY vaccine, expanded protection can be provided. The first option is to replace primary MenC by a MenACWY vaccine in infants, which is likely to be cost-saving when the negotiated price in a tender is lower for a MenACWY than for the MenC vaccine.[17] However, this strategy does not target the waning of antibody levels after primary infant immunisation. Furthermore, the changing epidemiology of MenY and MenW IMD (including outbreaks and slight increases of incidence in several other countries) is affecting healthy people in all age-groups. Therefore, to target the waning immunity and indirectly prevent IMD in all age-groups, the second option is to introduce a MenACWY booster dose in adolescents. A MenACWY booster results in high immune responses that are comparable with a MenC booster, irrespectively of how it is conjugated.[18,19,27] With the current Dutch epidemiology, a MenACWY booster is unlikely to be cost-effective.[17] However, with the changing epidemiology in mind, a MenACWY booster provides broader protection, is likely to be cost-effective and has positive effects on herd protection.[17] In addition, the aforementioned cost-effectiveness analyses are based on the list-price of the vaccine. When vaccines are used programmatically, tenders can significantly reduce the price of a vaccine to be cost-effective.

In Canada, the United States, the United Kingdom, Austria, and Greece a MenACWY vaccine already is or will be implemented in their NIPs as primary immunisation and/or booster to maintain low carriage rates and enlarge meningococcal serogroups protection beyond MenC IMD (Table).[18,22,26] Moreover, as United Kingdom's rise in MenW IMD (22 in 2009 and 117 in 2014) includes the same virulent strain (ST-11) that caused the outbreak of MenC IMD 15 years ago[28] and this same MenW clone was causing the epidemics in South America with high case-fatality ratios,[29] the United Kingdom recently decided to replace their MenC adolescent booster by a MenACWY booster and subsequently perform a catch-up campaign for students to take out carriage and induce herd protection. Because the 4CMenB infant vaccine provides some protection against the ST-11 strain due to a common subcapsular antigen, and the need for multiple doses of MenACWY vaccine in infancy, the United Kingdom decided not to implement the MenACWY vaccine in their infant immunisation programme.[23] To conclude, implementation of a MenACWY booster would enlarge the IMD protection and target the waning immunity after primary MenC immunisation.

Targeting Greatest Burden of Disease by Introducing an Infant MenB Vaccine

MenB IMD still has the highest burden of disease amongst infants in the Netherlands. Implementation of the recent available 4CMenB vaccine in the NIP should be considered. Moreover, it has been demonstrated that the burden of disease is not negligible as elevations of MenB IMD occur with intervals of 10-25 years.[16] Furthermore, despite discussion about the strain-coverage of the 4CMenB vaccine, research showed that the theoretical effectiveness is sufficient.[30-32] The 4CMenB vaccine is licensed from 2 months of age.[7] In contrast, the LP2086 vaccine licensed in the United States is only approved for individuals 10-25 years of age and not for the patient-population in which the highest burden is found.[33] The first regional MenB immunisation campaign globally, using 4CMenB, has been realised in 2014 in Quebec, Canada.[34] Also, the United Kingdom has recently decided to introduce the 4CMenB vaccine for infants administered on a 2, 4 + 12-13 months (2+1) schedule (Table).[31,35] Although the price is not made official, it seems unlikely that it is implemented at a cost-effective price.[36] With the current relatively low incidence of MenB IMD in the Netherlands, 4CMenB, was found unlikely to be cost-effective, when administered on a 2, 3, 4 + 11 months (3+1) schedule.[37] Considering, however, the periodicity of MenB IMD, the indirect costs of sequelae and the possibility to administer at a 2+1 schedule are included in cost-effectiveness analyses, MenB IMD has the potential to be cost-effective. In addition, clinical studies reported fevers after administration of the 4CMenB vaccine.[38] Still, this side effect can be combatted by administration of paracetamol and does not outweigh the health benefits.[39] Another possible advantage of the 4CMenB vaccine is that there are indications that it provides protection against additional serogroups, referred to as cross-immunity. To conclude, MenB IMD has the highest prevalence and can now be targeted by implementing an infant MenB vaccine.

Recommended Action

Optimisation of the immunisation strategy should be considered, because the changing epidemiology of IMD potentially targets an extensive group in the near future. Since the introduction of the MenC vaccine was successful, IMD currently has a relatively low incidence. However, the epidemiology is changing.

From a public health benefit oriented perspective several conclusions can be drawn. In order to target IMD in the foreseeable future, combat antibiotic resistance and reduce healthcare expenditures in industrialised countries, implementation of additional IMD vaccines in the NIP should be considered. To illustrate, in the Netherlands, introduction of a MenB vaccine in infants has priority as it would target the highest burden of disease and combat the periodicity of MenB IMD. Thereafter, it is important to target the waning antibody levels after primary MenC immunisation, which can be done by introducing a MenC adolescent booster. Then, monitoring and surveillance of IMD should pay extra attention to the additional serogroup occurrences in order to combat possible abrupt rises in incidence. Therefore, an

alternative scenario is to introduce a MenACWY adolescent booster, which would provide long-term protection that goes beyond MenC prevention. With the changing epidemiology in mind, it is likely that a MenACWY booster is as (cost-) effective as a MenC booster.

Implications for Invasive Meningococcal Disease Prevention

Taking into account the burden of meningococcal disease and the latest scientific knowledge related to IMD and prevention, it appears that in the near future the epidemiology of IMD will change. Immunisation remains the best way to prevent IMD and additionally reduces healthcare expenditures and the use of antibiotics. The present paper suggests options to improve the current immunisation policies.

Acknowledgements

This paper is a result of a research internship part of the MSc Management, Policy Analysis and Entrepreneurship in Health and Life Sciences at the VU University, Amsterdam, The Netherlands. GlaxoSmithKline BV was the commissioner of this study and supported in material and information. GlaxoSmithKline BV played no part in data collection and interpretation. JB received a small financial intern compensation of GlaxoSmithKline BV. Additional information was received from the Health Council of the Netherlands and Public Health England.

Ethical issues

Not applicable.

Competing interests

Potential conflicts of interest are disclosed in the Acknowledgement section.

Authors' contributions

Study concept and design (JCMB); acquisition of data (JCMB); analysis and interpretation of data (JCMB); drafting of manuscript (JCMB); critical revision of the manuscript for important intellectual content (JR); approval of final version (JCMB and JR).

References

1. Ali A, Jafri RZ, Messonnier N, et al. Global practices of meningococcal vaccine use and impact on invasive disease. *Pathog Glob Health.* 2014;108(1):11-20. doi:10.1179/2047773214Y.0000000126
2. McIntosh ED, Carey V, Toneatto D, Dull P, Wassil J. Prevention of rare diseases: how revolutionary techniques can help vulnerable individuals-the example of serogroup B meningococcal infection. *Ther Adv Vaccines.* 2015;3(1):13-23. doi:10.1177/2051013614557477
3. Whelan J, Bambini S, Biolchi A, Brunelli B, Robert-Du Ry van Beest Holle M. Outbreaks of meningococcal B infection and the 4CMenB vaccine: historical and future perspectives. *Expert Rev Vaccines.* 2015;14(5):713-736. doi:10.1586/14760584.2015.1004317
4. European Medicines Agency (EMA). European Medicines Agency recommends approval of first vaccine for meningitis B. Vaccine to provide broad coverage against meningococcal group B infections (press release); 2012.
5. Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. *Vaccine.* 2012;30(suppl 2):B3-B9. doi:10.1016/j.vaccine.2011.12.062
6. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. *Lancet.* 2007;369(9580):2196-2210. doi:10.1016/S0140-6736(07)61016-2
7. Safadi MA, Bettinger JA, Maturana GM, Enwere G, Borrow R. Evolving meningococcal immunization strategies. *Expert Rev Vaccines.* 2015;14(4):505-517. doi:10.1586/14760584.2015.979799
8. European Centre for Disease Prevention and Control (ECDC). *Surveillance of invasive bacterial disease in Europe, 2012. Invasive pneumococcal disease, invasive Haemophilus influenza disease and invasive meningococcal disease*. Stockholm: ECDC; 2015.
9. Jorgensen JH, Crawford SA, Fiebelkorn KR. Susceptibility of Neisseria meningitidis to 16 antimicrobial agents and characterization of resistance mechanisms affecting some agents. *J Clin Microbiol.* 2005;43(7):3162-3171. doi:10.1128/JCM.43.7.3162-3171.2005
10. Lockyer K, Gao F, Derrick JP, Bolgiano B. Structural correlates of carrier protein recognition in tetanus toxoid-conjugated bacterial polysaccharide vaccines. *Vaccine.* 2015;33(11):1345-1352. doi:10.1016/j.vaccine.2015.01.046
11. de Voer RM, Mollema L, Schepp RM, et al. Immunity against Neisseria meningitidis serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. *PLoS One.* 2010;5(8):e12144. doi:10.1371/journal.pone.0012144
12. Broker M, Jacobsson S, DeTora L, Pace D, Taha MK. Increase of meningococcal serogroup Y cases in Europe: a reason for concern? *Hum Vaccin Immunother.* 2012;8(5):685-688. doi:10.4161/hv.20098
13. Broker M, Jacobsson S, Kuusi M, et al. Meningococcal serogroup Y emergence in Europe: update 2011. *Hum Vaccin Immunother.* 2012;8(12):1907-1911. doi:10.4161/hv.21794
14. Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960-2012: an analysis of national surveillance data. *Lancet Infect Dis.* 2014;14(9):805-812. doi:10.1016/S1473-3099(14)70806-0
15. Ruitenberg EJ, Houweling H. [Universal vaccination against group-C meningococci and pneumococci; summary of the advice from the Health Counsil of the Netherlands]. *Ned Tijdschr Geneeskd.* 2002;146(20):938-940.
16. Van der Ende A, Spanjaard L. *Bacterial Meningitis in the Netherlands; Annual Report 2013*. Amsterdam: Netherlands Reference Laboratory for Bacterial Meningitis (AMC/RIVM); 2014.
17. Hepkema H, Pouwels KB, van der Ende A, Westra TA, Postma MJ. Meningococcal serogroup A, C, W(1)(3)(5) and Y conjugated vaccine: a cost-effectiveness analysis in the Netherlands. *PLoS One.* 2013;8(5):e65036. doi:10.1371/journal.pone.0065036
18. van 't Schurink-van 't Klooster TM. *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2013-2014*. National Institute for Public Health and the Environment (RIVM); 2014.
19. Stoof SP, van der Klis FR, van Rooijen DM, Knol MJ, Sanders EA, Berbers GA. Timing of an adolescent booster after single primary meningococcal serogroup C conjugate immunization at young age; an intervention study among Dutch teenagers. *PLoS One.* 2014;9(6):e100651. doi:10.1371/journal.pone.0100651
20. Mollema L, de Melker HE, Hahne SJM, van Weert JWM, Berbers GAM, van der Klis FRM. *PIENTER 2-Project: second research project on the protection against infectious diseases offered by the national immunisation program in the Netherlands*. National Institute for Public Health and the Environment (RIVM); 2009.
21. Kaaijk P, van der Ende A, Berbers G, van den Dobbelsteen GP, Rots NY. Is a single dose of meningococcal serogroup C

conjugate vaccine sufficient for protection? experience from the Netherlands. *BMC Infect Dis.* 2012;12:35. doi:10.1186/1471-2334-12-35
22. European Centre for Disease Prevention and Control (ECDC). Vaccine Schedule. http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx. Accessed August 12, 2015.
23. National Health Service (NHS) England. The NHS vaccination schedule. http://www.nhs.uk/Conditions/vaccinations/Pages/vaccination-schedule-age-checklist.aspx. Accessed August 12, 2015.
24. Centers for Disease Control and Prevention (CDC). Vaccines and Immunizations. Meningococcal: Who needs to be vaccinated? http://www.cdc.gov/vaccines/vpd-vac/mening/who-vaccinate.htm. Accessed August 12, 2015.
25. Public Health Agency of Canada. Canadian Immunization Guide. Part 4 Active Vaccines. Meningococcal Vaccine. Recommendations for Use. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-meni-eng.php. Accessed August 12, 2015.
26. Public Health England. Changes to the meningococcal C conjugate (MenC) vaccine schedule 2013-2015. Information for healthcare professionals. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/336171/MenC_information_for_healthcare_professionals_V7_.pdf. Accessed August 25, 2015. Published July 2014.
27. Ishola DA, Andrews N, Waight P, et al. Randomized Trial to Compare the Immunogenicity and Safety of a CRM or TT Conjugated Quadrivalent Meningococcal Vaccine in Teenagers who Received a CRM or TT Conjugated Serogroup C Vaccine at Preschool Age. *Pediatr Infect Dis J.* 2015. doi:10.1097/INF.0000000000000750
28. Ladhani SN, Beebeejaun K, Lucidarme J, et al. 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(4):578-585. doi:10.1093/cid/ciu881
29. Lucidarme J, Hill DM, Bratcher HB, et al. Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. *J Infect.* 2015. doi:10.1016/j.jinf.2015.07.007
30. Medini D, Stella M, Wassil J. MATS: Global coverage estimates for 4CMenB, a novel multicomponent meningococcal B vaccine. *Vaccine.* 2015;33(23):2629-2636. doi:10.1016/j.vaccine.2015.04.015
31. Drysdale SB, Pollard AJ. Group B meningococcal vaccine science and policy. *J Infect.* 2015;71(suppl 1):S15-S20. doi:10.1016/j.jinf.2015.04.021
32. Vogel U, Taha MK, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. *Lancet Infect Dis.* 2013;13(5):416-425. doi:10.1016/S1473-3099(13)70006-9
33. Food and Drug Administration (FDA). FDA News Release: First vaccine approved by FDA to prevent serogroup B Meningococcal disease. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm420998.htm. Accessed May 15, 2015. Published October 29, 2014.
34. Novartis (2015). Bexsero® vaccine approved by FDA for the prevention of meningitis B, a leading cause of bacterial meningitis in the US [news release]. https://www.novartis.com/news/media-releases/novartis-bexsero%C2%AE-vaccine-approved-fda-prevention-meningitis-b-leading-cause. Accessed February 5, 2015. Published January 23, 2015.
35. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine.* 2013;31(23):2638-2646. doi:10.1016/j.vaccine.2013.03.034
36. Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. *BMJ.* 2014;349:g5725. doi:10.1136/bmj.g5725
37. Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GP, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: Crucial impact of changes in incidence. *Hum Vaccin Immunother.* 2013;9(5):1129-1138. doi:10.4161/hv.23888
38. Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet.* 2013;381(9869):825-835. doi:10.1016/S0140-6736(12)61961-8
39. Public Health England. Vaccine update. Issue 230, June 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/443262/PHE_9402_VU230_June_2015_11_web.pdf. Accessed July 27, 2015.