## Norwegian Institute of Public Health, Division of Infection Control, Case number 2

| |
|---|
| **Institution:** Norwegian Institute of Public Health (NIPH) |
| **Administrative unit:** Division for Infection Control |
| **Title of case study:** Impact of vaccination on meningococcal disease |
| **Period when the underpinning research was undertaken:** 2012-2022 |
| **Period when staff involved in the underpinning research were employed by the submitting institution:** 2012-2022 |
| **Period when the impact occurred:** 2012-2022 and ongoing into 2023-2024 |

**1. Summary of the impact** (indicative maximum 100 words).

The rollout of a new polysaccharide-conjugated vaccine against serogroup A meningococcal disease in countries of sub-Saharan Africa, with more than 300 million people vaccinated is estimated to have avoided 300,000 cases and 30,000 deaths. Our research on the transmission of the pathogen and on its genetic evolutionary capability, as well as on the ability of the vaccine to induce mucosal immunity, has contributed to demonstrate how the vaccine generated herd protection of the populations and prevented serogroup A epidemics since its introduction. In Norway, our studies have pin-pointed the need for introducing meningococcal vaccine among teenagers, impacting national guidelines.

**2. Underpinning research** (indicative maximum 500 words)

Meningococcal disease, a public health threat in all countries of the world, is caused by the bacterium *Neisseria meningitidis* (the meningococcus). Research on meningococcal disease and vaccines have been a focus area at NIPH for several decades. NIPH is a World Health Organization (WHO) Collaborating Centre for Meningococci.

Meningococci are harboured only by humans, who are normally colonized asymptomatically in the oropharynx. Occasionally, the bacterium can reach the bloodstream and/or the meninges and cause severe disease. Six serogroups (A, B, C, W, X and Y) of *N. meningitidis* are responsible for nearly all cases globally. Various vaccines have been developed.

The highest burden of the disease is in sub-Saharan Africa (the meningitis belt) where large serogroup A epidemics have occurred for many decades. An effective and affordable polysaccharide-conjugated vaccine against serogroup A (MenAfriVac) was developed and introduced in sub-Saharan Africa from 2010. Polysaccharide-conjugated vaccines can potentially hinder carriage acquisition, reducing transmission of the bacterium in the population, and thus also providing protection of the non-vaccinated individuals (herd protection). This is a most significant public health impact of the use of conjugate vaccines.

To demonstrate that herd protection was provided by MenAfriVac, we performed, in collaboration with WHO and the Centers for Disease Control and Prevention in the United States (CDC), large carriage studies at multiple sites in Burkina Faso, before and after the vaccine introduction (Kristiansen et al., 2013). These studies were in large part supported by grants from the Research Council of Norway (RCN). Oropharyngeal samples were collected from nearly 50,000 people in the age-group 1 to 29. In-depth analyses of the isolated bacteria were performed at the NIPH using cutting-edge methods, including sequencing of selected genes. From 2016 whole genome sequencing was established and applied to all meningococcal isolates recovered from the surveys (Brynildsrud et al., 2018).

Furthermore, genetic loci involved in protein glycosylation were analysed in collections of isolates from meningococcal patients and carriers, as protein glycosylation is thought to play a significant role in adaptation of the bacteria in response to the environment. Large degree of

microheterogeneity in protein glycan structure was evidenced, possibly contributing to the ability of *N. meningitidis* to resist the bactericidal activity of human serum (Børud et al., 2020). To evaluate the immunological effect of conjugate vaccines in both serum and saliva, a rapid and simple multiplex microsphere assay for the quantification of specific IgG and IgA antibodies against meningococcal serogroup A, C, W, and Y capsular polysaccharides was developed. The assay was found to be reproducible, showing a good correlation with standard methods to measure antibodies, while requiring less time and workload (Bårnes et al., 2015). In Norway, adolescents are at increased risk of meningococcal carriage and disease, as in many other countries. Our study showed that meningococcal carriage is high among older teenagers and the ACWY vaccine would protect against most circulating disease-causing strains (Watle et al., 2020). Cost-effectiveness analysis evidenced that introducing the vaccine for adolescents in the national immunisation program would likely be cost-effective (Watle et al., 2021).

**Key researchers, position (years of employment)**

- Ola Brynildsrud, scientist (2015-ongoing)
- Bente Børud, senior scientist (2013-ongoing)
- Guro Bårnes, PhD student (2012-2017)
- Dominique A. Caugant, chief scientist (2012-ongoing)
- Hannah Jørgensen, scientist (2013-2016)
- Paul Kristiansen, PhD student/scientist (2012-2019)
- Lisbeth M. Næss, senior scientist (2012-ongoing)
- Gro Tunheim, senior scientist (2017-ongoing)
- Sara V. Watle, senior physician/PhD student (2017-ongoing)

**3. References to the research** (indicative maximum of six references)

Watle SV, Næss LM, Tunheim G, Caugant DA, Wisløff T. Cost-effectiveness of meningococcal vaccination of Norwegian teenagers with a quadrivalent ACWY conjugate vaccine. Hum Vaccin Immunother. 2021 Aug 3;17(8):2777-2787. doi: 10.1080/21645515.2021.1880209.

Watle SV, Caugant DA, Tunheim G, Bekkevold T, Laake I, Brynildsrud OB, Næss LM. Meningococcal carriage in Norwegian teenagers: strain characterisation and assessment of risk factors. Epidemiol Infect. 2020 Mar 31:148:e80. doi: 10.1017/S0950268820000734.

Brynildsrud OB, Eldholm V, Bohlin J, Uadiale K, Obaro S, Caugant DA. Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. Proc Natl Acad Sci U S A. 2018 May 22;115(21):5510-5515. doi: 10.1073/pnas.1802298115.

Børud B, Bårnes GK, Brynildsrud OB, Fritzsønn E, Caugant DA. Genotypic and Phenotypic Characterization of the *O*-Linked Protein Glycosylation System Reveals High Glycan Diversity in Paired Meningococcal Carriage Isolates. J Bacteriol. 2018 Jul 25;200(16):e00794-17. doi: 10.1128/JB.00794-17.

Bårnes GK, Kristiansen PA, Caugant DA, Næss LM. Development and Evaluation of a Multiplex Microsphere Assay for Quantitation of IgG and IgA Antibodies against Neisseria meningitidis Serogroup A, C, W, and Y Polysaccharides. Clin Vaccine Immunol. 2015 Jul;22(7):697-705. doi: 10.1128/CVI.00087-15.

Kristiansen PA, Diomandé F, Ba AK, Sanou I, Ouédraogo AS, Ouédraogo R, Sangaré L, Kandolo D, Aké F, Saga IM, Clark TA, Misegades L, Martin SW, Thomas JD, Tiendrebeogo SR, Hassan-King M, Djingarey MH, Messonnier NE, Préziosi MP, Laforce FM, Caugant DA. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. Clin Infect Dis. 2013 Feb;56(3):354-63. doi: 10.1093/cid/cis892.

**4. Details of the impact** (indicative maximum 750 words)

It was essential to determine whether MenAfriVac was also providing herd protection, as was the case for a monovalent serogroup C conjugate vaccine introduced in the UK in 1999. MenAfriVac has been introduced gradually since 2010 in mass vaccination campaigns in 24

countries of the meningitis belt and 15 countries have introduced the vaccine into the national immunisation programmes. Since 2017 there have been no confirmed cases of serogroup A disease in countries of the meningitis belt. Our studies on carriage showing the dramatic effect of the vaccine on transmission were crucial in explaining the impact of the vaccination campaigns. Since the introduction of MenAfriVac, the overall incidence of meningitis in the meningitis belt has decreased steadily and no serogroup A cases occurred either in the unvaccinated population younger than 1 year and older than 30 years that were not eligible for vaccination.

Although serogroup A epidemics have been eliminated, a serogroup C epidemic broke out in Nigeria starting in 2013. In 2015 the epidemic spread to Niger resulting in about 10,000 cases that year. The epidemic is still ongoing in the region in spite of reactive vaccination campaigns. We showed that this serogroup C epidemic was caused by a strain, not known to have caused disease previously, that originated from an ancestor previously circulating asymptomatically in carriers in the African population. The ancestral strain acquired several virulence factors, including a serogroup C polysaccharide capsule. Whole genome sequencing allowed to pin-point to the genetic events that had occurred in the ancestral strain, resulting into this emerging highly virulent pathogen. A pentavalent conjugate vaccine (ACYWX) that might cover this new strain, as well as others, is now WHO pre-qualified and carriage studies to assess the herd protection impact of this new vaccine are under planning.

Currently available meningococcal vaccines protect against most disease-causing strains, but not all, and duration of protection is not lifelong. Glycosylation is an important protein modification system displayed by bacteria that is used to evade the human immune response. Ongoing studies (2019-present) will determine whether glycan-specific antibodies can confer protection against meningococcal infection. This could be important for the development of new, improved neisserial vaccines, including vaccines against gonococcal infection.

The multiplex microsphere immunoassay developed for antibody detection in serum and saliva was used to test the effect of both the monovalent serogroup A MenAfriVac and a tetravalent serogroup A, C, W and Y conjugate vaccine in Ethiopian volunteers. With the use of this assay, we could show that serogroup-specific IgG antibody levels in serum increased with both vaccines. In addition, we could show that vaccination with MenAfriVac elicited specific salivary antibodies, giving a biological explanation for the vaccine's effectiveness against carriage. The multiplex method was also used to show that natural protection against meningococcal disease is low among unvaccinated Norwegian adolescents.

In Norway, vaccination with a serogroup ACWY polysaccharide conjugate vaccine has been recommended for teenagers since 2011, when an increase in meningococcal disease was observed in this age group. While recommended, the vaccine is not included in the national immunisation programme, potentially contributing to social inequity in health. Serogroup Y was the predominant serogroup circulating in this age-group, as determined by our carriage surveys, but unvaccinated adolescents had low natural immunity against this serogroup. Use of Swedish snus (smokeless tobacco), kissing and partying were associated with carriage. These results have had consequences for Norwegian guidelines, underpinning the need for vaccination of this age group, and have been communicated to the public and health care personnel involved in meningococcal vaccination of adolescents. The results will also be important for evaluating whether meningococcal vaccination should be included for teenagers in the national immunisation program. Therefore, our studies in Norway have been the basis for moving forward such a recommendation to the Ministry of Health.

Our studies on meningococcal vaccines and vaccination have a significant impact on public health both nationally and globally. Our contribution to the projects in Africa has been

important to explain how the vaccines are working and to give confidence in new development and implementation. Altogether our research is a support to the WHO global road map for defeating meningitis by 2030 through the elimination of bacterial meningitis epidemics.

**5. Sources to corroborate the impact** (indicative maximum of ten references)

The impact of our studies has been acknowledged by international stakeholders such as the WHO https://iris.who.int/bitstream/handle/10665/342010/9789240026407-eng.pdf?sequence=1 and the Meningitis Research Foundation https://www.meningitis.org/blogs/using-technology-to-defeat-meningitis. We demonstrated for the first time that MenAfriVac was highly effective in reducing transmission of serogroup A meningococci by preventing carriage https://pubmed.ncbi.nlm.nih.gov/22607898/. This indicated that if vaccination was given to all countries of the meningitis belt, epidemics of serogroup A disease could be eliminated. The findings were essential to give confidence to the international community to invest and accelerate the introduction of the vaccine. Four years after the beginning of the introduction significant reduction of the disease burden was evidenced, linked to nearly elimination of the bacterium in the populations having introduced the vaccine https://pubmed.ncbi.nlm.nih.gov/26553676/. The results have been pivotal in evaluating strategies for introduction of MenAfriVac in the national immunisation programmes of the countries of the meningitis belt https://pubmed.ncbi.nlm.nih.gov/29364884/. For planning the introduction of the pentavalent (ACWXY) vaccine, the results are essential to determine the age-group of the population to vaccinate to attain the maximum impact at the lower cost.

The results from the NUSS-study have been disseminated to the public in Norway through a dedicated website https://www.fhi.no/ss/studier/nuss-studien/publikasjoner-fra-nuss-studien/ and national media (newspapers, radio, television) https://www.tv2.no/nyheter/innenriks/sykdommen-kan-vaere-dodelig-likevel-far-ikke-alle-vaksinen-gratis/15272031/, as well as at national and international conferences for health care personnel and researchers working in the meningococcal field https://www.fhi.no/globalassets/bilder/vaksine/vaksinedagene-2019-forelopig-program.pdf, https://emgm.eu/meetings/emgm2019/emgm2019_abstracts.pdf, https://www.ipnc2022.co.za/.The results have also been included in a health technology assessment initiated in 2022, evaluating whether meningococcal vaccine for teenagers should be included in the national immunisation programme in Norway. A new recommendation from the NIPH is now under evaluation by the Norwegian Ministry of Health and Care Services.