Policy Brief

Neisseria meningitidis serogroup X (a New serogroup) and W_{135} are detected in Ethiopian bacterial meningitis patients

Background

The population living in countries of the meningitis belt of Africa stretching from Senegal in the west to Ethiopia in the east are facing frequent epidemics of meningitis. The first report on the outbreak of meningitis in Africa was documented in 1840 (1). Major epidemics of meningitis were reported earlier in African countries such as Nigeria and Ghana in 1905-1908 and in Ethiopia in 1901 and 1935 (2). Since 1935, no single decade has passed without occurrence of meningitis epidemic in Ethiopia,and the most recent epidemics occurred in 2000 and 2003 (3,4,5). In the past two decades, the dominant meningococcal serogroup causing the disease in the meningitis belt countries was mainly serogroup A (4, 6, 7), followed by serogroup C (8, 3). However, the presence of other serogroups wasreported from meningitis belt countries in later years (3).

Emergence of new serogroup

Studies are reporting about emergence of serogroup X meningococci which previously have been considered a rare cause of sporadic meningitis. Outbreaks of serogroup X meningitis occurred in Niger, Uganda, Kenya, Togo and Burkina Faso during 2006–2010. Neither serogroup X nor serogroup W have caused an epidemic wave of the scale of serogroup A reported from Burkina Faso in 1996–1997 and during 2002 (9). Following the recent introduction of a glycoconjugate vaccine against serogroup A, epidemiology of meningococcal meningitis in Africa is changing rapidly. Currently Africa is vulnerable to the new epidemics of meningococcal serogroup X meningitis since no vaccine is available against the referred serogroup (10). Increased mobility of people has impacted spread of the disease from one geographical location to another (11). This is one of the reasons for altered pictures of meningococcal meningitis serogroup distribution across the globe (5).

Neisseria meningitidis vaccine coverage

Neisseria meningitidis vaccine coverage comprising serogroups A and C is implemented when there is a report about occurrence of epidemic of the disease, i.e., 10-15 patients with the disease within one-week duration from a population of 100,000. Durations between the end of November and the end of June are involving seasonal cycles of epidemics of meningitis. This occurs especially at the regions which enclose the meningitis

belt where meningococcal disease occurs in epidemic cycles lasting between 8 to 15 years (12). However, if the disease occurs in patients below the referred number, it is considered as non-epidemic or a sporadic event.

Anti-meningococcal meningitis serogroup A vaccine (MenAfrivac) was administered in the meningitis belt countries from 2010-2015 for age groups 1-29 with the aim of lowering frequency of meningitis epidemics. Substantial reduction of incidence of meningitis is reported from the belt countries after administration of MenAfrivac. Studies on meningococcal meningitis are mainly focused inthe epidemic season of the disease, while less attention is given to non-epidemic season. Serogroups of *N. meningitidis* that were not reported in a certain geographical region may be detected in meningococcal meningitis patients in another geographic region during non-epidemic season or epidemic season. Transmission of the serogroup could occur from one season to another (13). Great difficulty is faced by most countries with regard to showing appropriate response to the demands needed for control and prevention of the epidemic. This may hinder evidence-based immunization policy (7).

Socioeconomic impacts and control of meningococcal epidemics

Poor living conditions, overcrowded housing are some of the factors linked to a higher incidence of meningococcal disease. This may disrupt routine health care services and other important related activities (14). A multi-disciplinary overview of the determinants of meningitis transmission dynamics and possible disease causation may be important strategies towards inputs for controlling disease occurrence in the African meningitis belt (15). Sporadic occurrences of meningitis and its epidemics may be lowered through population immunization for specific serogroups that are detected among the diseased population. Although immunization of a population may need to be visualized from different angles such as carriage rate of healthy population, social and economic backgrounds of the society, preparing the next generation vaccine for the serogroups on the stage is inevitable (16). Additional efforts on considering socioeconomic factors, social behavior, climate and environmental factor, demography, respiratory tract disease and geographical localization contribute towards disease control strategies at the African meningitis belt (17).

Neisseria meningitidis is the major cause of seasonal meningitis epidemics in the African meningitis belt. In the changing context of a reduction in incidence of serogroup A and an increase in incidence of serogroups W and C, a better understanding of the determinants driving the disease transmission dynamics remains crucial to improving bacterial meningitis control.

Study on bacterial meningitis in Ethiopia during non-epidemic seasons: 2012-2013

We carried out a study focusing ondetection of etiologic agents of bacterial meningitis during non-epidemic seasonsfrom 2012-2013 in Ethiopia, among patients clinically diagnosed with bacterial meningitis in three referral university hospitals (Gondar, Hawassa and Tikur Anbessa Teaching University hospitals). One hundred thirty-nine patients with age range of 2 days to 72 years old comprising 56 females and 83 males participated in the study. The study has obtained ethical clearance from national and institutional ethical review committees. Informed consent from the patients or guardians (on behalf of under 18 patients) and assent from children above age 12 were obtained for inclusion in the study.

Neisseria meningitidis serogroup X (newly detected, i.e., which was not reportedinEthiopia among bacterial meningitis patients) and serogroup W_{135} which occurred frequently in the current study (as not reported from previous studies in the country) were found in the CSF of the patients. Improving the knowledge about meningitis and meningococcal vaccine needs a high impact input through elevating the dynamics of awareness of the population. This occurs through making alliance between public health representatives and media with

evidence-based information (18).

The newly identified serogroup X (from Ethiopian meningitis patients) and the frequently occurred serogroup W_{135} were detected with highly sensitive molecular detection method carried out at Armauer Hansen Research Institute (AHRI) and the Norwegian Institute of Public Health (NIPH/Oslo, Norway). Other bacterial etiologic agents such as *Streptococcus pneumoniae* as well as *Haemophilus influenzae* (14) of meningitis were also diagnosed among the 139 patients who visited the hospitals.Using the highly sensitive real time PCR method, the study detected a total of 27 *N. meningitidis* bacteria (comprising serogroups 1 X, 7 W_{135}, 11 A, 1 C and 7 non-groupable) from a total of 27/139 (19.4%) CSF samples. Each CSF sample collected from the patient was aliquoted into transportation medium supporting survival of the microbes (19). The samples were sent to AHRI laboratory for a parallel less sensitive test (culture detection) in the bacteriology lab of the institute. Through the use of culture detection assay we found 5 *N. meningitidis* (4 A and 1 W_{135} serogroups) from a total of 139 (3.6%) patient CSF samples. The result from the less sensitive culture detection method has under-estimated the outcome more than five times compared to the highly sensitive real time PCR method. The newly detected (X) and frequently occurred (W_{135}) meningococcal serogroups were not detectedwith the culture method. Poor sample handling in the clinical laboratories, may affect the culture detection test as also reported from other studies (4).

Aim of this policy brief (based on the outcome of the study)

The intention of this policy brief is to inform possible future strategies on how to address the challenges of lower detection of the etiologies of bacterial meningitis and to plan for anti-meningococcal vaccination comprising additional serogroups to the existing serogroup a vaccine. Formal decision-making process with regard to adoption of vaccines to control the vaccine-preventable diseases such as meningitis based on research-based evidences needs mapping and analyzing the formal decision-making process. This goes towards introduction of new vaccines encompassing the detected serogroups of the etiologic agents of the disease within the context of health policy and health systems and identify the ways of making decisions to uptake new vaccines in the country (8).

Major points extracted from the outcomes of the study

The following findings extractedfrom ourresearch on bacterial meningitis among patients clinically diagnosed with pyogenic meningitis during the non-epidemic season need to be considered to improve diagnosis, vaccine design and improving technical competence:

I Selecting or designing meningococcal vaccine comprising serogroups A, W_{135}, C as well as Y , and X as also suggested by other studies carried out in Kenya, Uganda and several West African countries .

II Availing trans-isolate media (TIM) to hospitals and health centers located in remote areas to transport CSF samples from bacterial meningitis suspected patient to referral hospital laboratory where culture detection set up is available.

III Upgrading laboratory capacity of the national referral lab for using the sensitive lab detection for suspected meningitis samples from all over the country to establish a database to be used as a reference for vaccine selection and tailoring.

IV Providing a refresher training for health care workers on good clinical laboratory practice on how to handle emergency samples (such as CSF) to conduct faster culture diagnosis.

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References

1. Codjoe, S.N., Nabie, V.A. (2014). Climate change and cerebrospinal meningitis in the Ghanaian meningitis belt. *Int J Environ Res Public Health.* **11**(7): 6923-6939.

2. Castellani, A. (1939). La meningitecerebro-spinalendemique en Afrique orientale Italienne. *Bull OffIntHyg Publ*. **31**: 455-456.

3. Chanteau, S., Dartevelle, S., Mahamane, A. E., Djibo, S., Boisier, P., Nato, F. (2006). New rapid diagnostic tests for *Neisseria meningitidis* serogroups A, W135, C, and Y. *PLoSMed*.**3**(9): e337.

4. Gudina, E. K., Tesfaye, M., Adane, A., Lemma, K., Shibiru, T., Pfister, H. W., & Klein, M. (2016). Challenges of bacterial meningitis case management in low income settings: an experience from Ethiopia. *Trop Med IntHealth*. 21(7): 870-878.

5. Norheim, G., Rosenqvist, E., Aseffa, A., Yassin, M.A., Mengistu, G., Kassu, A., Fikremariam, D., Tamire, W., Høiby, E.A., Alebel, T. (2006). Characterization of *N. meningitidis* isolates from recent outbreaks in Ethiopia and comparison with those recovered during the epidemic of 1988 to 1989. *J ClinMicrobiol.* 44 (3): 861-871.

6. Habte-Gabriel, E., Tekle, E., Mamo, M. (1984). Meningococcal meningitis in Ethiopia 1974–1983 and strategies of control. *Ethiop J Health Dev.* 1: 47-63.

7. Harrison, L. H., Pelton, S. I., Wilder-Smith, A., Holst, J., Safadi, M. A., Vazquez, J. A., Plotkin, S. A. (2011). The Global Meningococcal Initiative: recommendations for reducing the global burden of meningococcal disease. *Vaccine.* 29(18): 3363-3371.

8. Uddin, J., Sarma, H., Bari, T. I., Koehlmoos, T. P. (2013). Introduction of new vaccines: decision-making process in Bangladesh. *Journal of health, population, and nutrition*, *31*(2), 211.

9. Xie, O., Pollard, A. J., Mueller, J. E., Norheim, G. (2013). Emergence of serogroup X meningococcal disease in Africa: need for a vaccine. *Vaccine.* 31(27): 2852-2861.

10. Micoli, F., Romano, M. R., Tontini, M., Cappelletti, E., Gavini, M., Proietti, D., Balocchi, C. (2013). Development of a glycoconjugate vaccine to prevent meningitis in Africa caused by meningococcal serogroup X. Proceedings of the National Academy of Sciences. 110 (47): 19077-19082.

11. Al-Tawfiq, J.A., and Z.A. Memish. "The Hajj: updated health hazards and current recommendations for 2012." *Euro Surveill*. 17(41): 20295.

12. Mihret, W. PhD Thesis, (2017). Etiology, Disease Severity and Diagnostic Challenges of Bacterial Meningitis during Non-epidemic Seasons in Ethiopia: 2012-2013.

13. Haimanot, R.T., Caugant, D.A., Fekadu, D., Bjune, G., Belete, B., Frøholm, L.O., Høiby, E.A., Rosenqvist, E., Selander, R.K., Bjorvatn, B., (1990). Characteristics of serogroup A *N. meningitidis* responsible for an epidemic in Ethiopia, 1988-89. *Scand J Infect Dis.* 22 (2): 171-174.

14. Mago, Vijay K., Ravinder Mehta, Ryan Woolrych, Elpiniki I. Papageorgiou (2012). "Supporting meningitis diagnosis amongst infants and children through the use of fuzzy cognitive mapping*." BMC Med Inform DecisMak.* 12 (1). 1472-6947.

15. Christensen, H., May, M., Bowen, L., Hickman, M., & Trotter, C. L. (2010). Meningococcal carriage by age: a systematic review and meta-analysis. *The Lancet infectious diseases.* 10(12): 853-861.

16. Caugant, D.A., and Maiden, M.C. (2009). Meningococcal carriage and disease-population biology and evolution. *Vaccine.* 27*:* B64-B70.

17. Umaru, Emmanuel Tanko, Ahmed Nazri Muhamad Ludin¹ Mohammed Rafee, Majid Soheil Sabri Chingle Moses P, Wallace (2013). EnegbumaAbdrazack Nelson Tajudeen A, and Malaysia Bahru. "Risk Factors Responsible for the Spread of Meningococcal Meningitis: A Review." 1 (2): 1-30.

18. Zanardini, E., M. Moneda, E. Croce, L. Covolo, E. Ceretti, U. Gelatti (2017). "Talking about meningitis. How is the quality of online newspapers information? An Italian studyLoredanaCovolo." *Eur J Public Health* 27, no. suppl_3.

19. Mihret, W., Lema, T., Merid, Y., Kassu, A., Abebe, W., Moges, B., Tenna A., Woldegebriel, F., Yidnekachew, M., Mekonnen, W., Ahmed, A., Yamuah, L., Silamsaw M., Petros B., Oksnes, J., Rosenqvist, E., Ayele, S., Aseffa, A., Caugant, D., Norheim, G. (2016). Surveillance of Bacterial Meningitis, Ethiopia, 2012–2013. *Emerg Infect Dis.* 22 (1):75-78.