World Health Organization

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Serogroup C in the Meningitis Belt:

Facing the Challenge

Report of meeting held in Geneva, October 2015

1. Introduction

A meeting of an expert group was held at WHO HQ, Geneva between 15 and 16 October 2015 to review experience from recent serogroup C meningococcal meningitis epidemics in Nigeria and Niger and to discuss ongoing risk and plans in relation to future epidemics (Annex A&B).

Conclusions on the risk assessment and on a review of prevention and control measures with recommendations are presented here.

2. Risk assessment: High risk of NmC epidemics across the meningitis belt

The first major NmC outbreak in the African meningitis belt since 1979 was seen in NW Nigeria in 2013. The epidemic expanded in this region in 2014 (1). In 2015, cases increased in number and geographically in NW Nigeria (S. Aliyu, K. Uadiale) but also with rapid expansion into Niger (H. Bouboucar, I. Alkassoum, S. Meyer). Numbers of confirmed serogroup C meningitis cases in the meningitis belt rose from 10 in 2013, to 48 in 2014, and to 1201 (to Week 39) in 2015. Nearly all these cases were in Nigeria and Niger. However some NmC cases (n=14) were also seen in Burkina Faso, Mali and Ivory Coast in 2015 (C. Lingani). Benin also reported one case, not included in the regional network.

The expert group concluded that there is a high risk of continuing expansion of serogroup C epidemics of meningococcal meningitis in 2016 and future years across the meningitis belt of sub-Saharan Africa.

Reasons for this assessment include:

- The epidemic continued to spread in Nigeria from 2013 to 2015 and expanded dramatically into Niger in 2015. The size of the outbreaks in Niger in 2015 showed similarities to previous explosive NmA outbreaks seen in that country (H. Boubacar)

- These NmC epidemics are caused by a unique clone (multilocus sequence type ST10217, clonal complex unassigned), genetically distant from all other invasive disease strains held at the WHO Collaborating Centre, NIPH, Oslo (D. Caugant). Two stored carriage isolates were found to have a related genetic profile, one non-serogroupable isolate from Burkina Faso in 2011, the other a serogroup C strain from Ghana in 2012. Two of the NmC disease strains

from Mali had a match for 5 or 6 MLST alleles and identical PorA to the ST-10217 clone (WHO Collaborating Centre, CDC Atlanta).

- Given that the last serogroup C epidemics in the meningitis belt were seen in the late 1970s (2), and that reactive campaigns with polysaccharide vaccines containing C have been very infrequent since 2011, population immunity to NmC across the belt is expected to be low.

The expert group considered that the re-emergence of NmC is likely due to natural evolutionary changes in the bacterial population rather than serogroup replacement following introduction of MenAfriVac. The reasons behind this conclusion are that (i) NmA carriage outside epidemics before the introduction of MenAfriVac was usually not detectable or at very low levels, leaving little opportunity for replacement of the bacterium in its ecological niche; (ii) large and rapid fluctuations in serogroup/strain distribution are known to occur in absence of vaccine intervention; (iii) the NmC outbreak strain is a completely new clone

3. Prevention and control strategies: Review

3.1. Vaccination

- Several different vaccine formulations containing serogroup C polysaccharide are potentially available to the International Coordinating Group (ICG), some as plain polysaccharide (AC, ACW, ACWY, BC), others as protein conjugate vaccines (ACWY, C) (A. Costa). The emergency stock of C containing vaccines available to the ICG is expected to be around 4 million doses by January 2016, despite ICG's efforts to secure 5 million doses.

- An affordable pentavalent conjugate vaccine (ACWXY) is being developed by the Serum Institute of India. Phase 1/2 trials are planned to start in 2016 in USA and Mali. The earliest availability of a licensed product for deployment in the meningitis belt is 2020 (M. Preziosi).

- Previous administration of a serogroup C containing polysaccharide vaccines blunts the immune response to a subsequent dose of another C polysaccharide vaccine. The immune response is also reduced, but to a lesser extent, if a C polysaccharide vaccine if followed by a C protein-polysaccharide conjugate vaccine. The implications of the observed reduction in immune response are not known. There is no evidence of any increase in susceptibility to disease. It is preferable to use conjugate rather than polysaccharide vaccines in all situations. (R. Borrow).

- Both quadrivalent (ACWY) and trivalent (ACW) polysaccharide vaccines were used in Niger this year. Although both vaccines showed a high short term effectiveness of >85%, the data suggested that effectiveness of the trivalent vaccine was less high than that of the quadrivalent vaccine. Differences in the W component of the two vaccines would need to be further explored as a possible factor to explain differences in effectiveness (M. Rondy).

- Some sales of relabelled time expired and fake vaccines were reported to the Ministry of Health in Niger (I. Alkassoum).

- Demands had been received for preventive vaccination with conjugate C vaccines before the next meningitis season. The difficulties of ensuring equitable vaccine distribution to all communities considered to be at risk were discussed, given a limited supply of vaccine. Many countries may consider themselves at risk, but prediction of risk by geographical area is very difficult.

3.2. Treatment and chemoprophylaxis

- Five days treatment was used successfully in Niger with a mix of hospital care for severe cases and community based ambulatory care for less severe cases (D. Job).

- Attack rates in household members after a case in Doutchi, Niger this year were 1760/100,000, 21 times higher than the corresponding rate for the district (M. Coldiron). The median interval between the date of admission of the first case and subsequent cases in the same household was 3 days.

3.3. Surveillance

- Surveillance of populations less than 100,000 is recommended by WHO in order to detect and respond promptly to local epidemics (3). A study in Niger showed that this would have improved the cost effectiveness of response to the 2015 NmC epidemic (H. Boubacar). Local area surveillance leading to local vaccination may be more efficient.

- The time taken in getting country permissions to send strains to the WHO collaborating centre reference laboratories led to several months delay in identifying the responsible strains.

- The revised alert threshold of 3/100,000 per week as recommended by WHO (2014) can sometimes buy lead in time (this was the case in 1 district in Niger and 2 LGA's in Nigeria, with 5, 3 and 1 weeks additional time respectively) (C. Trotter)

- Some countries e.g. Nigeria, Democratic Republic of Congo have relatively weak surveillance systems, others are stronger e.g. Burkina Faso, Niger. The MenAfriNet surveillance network is playing an important role in developing case based surveillance (S. Meyer).

- Although the performance of RDTs in detection of NmC has not been formally evaluated in the field, data from Nigeria showed a reasonable sensitivity 75% (95%CI 53-89%) and specificity 94% (95%CI 73-99%) of Pastorex testing compared to PCR and/or culture at NIPH, Oslo.

- A newly rapid diagnostic test (RDT) kit for ACWXY has been developed by the Institut Pasteur in Paris in partnership with BioSpeedia (M.Taha). It has three cassettes and requires a low volume of CSF (40 micro litres). It will be evaluated in Abidjan in 2016. Experience in Niger with the CERMES RDT has shown the importance of distribution to peripheral health centres (F. Sidikou).

4. Prevention and control strategies: Recommendations

4.1. Vaccination

- Protein conjugate vaccines or polysaccharide vaccines containing C can be used in response to confirmed NmC epidemics.

- If >= 30% NmW in mixed NmC/NmW epidemics, a vaccine containing C and W should be used following the principles for NmA/NmW outbreaks set out in the vaccine decision tree (WHO meningitis guide)

- Given the limited supply of C containing vaccines likely to be available at the beginning of the next meningitis season (January 2016) and the high risk of epidemics in more than one country, conjugate vaccines made available by the ICG should be kept for outbreak response and not used for preventive vaccination.

- The normally recommended age groups for targeted mass vaccination should be kept in outbreak response. Given the potential for carriage reduction after administration of conjugate vaccines, a restricted age group might be considered for mass vaccination with conjugate vaccines e.g. 5-15 or 2-19 years depending on vaccine availability and age distribution of cases.

- High priority should be given by partners to increasing the stockpile of C containing vaccines; UNICEF SD in particular should not restrict the procurement to prequalified vaccine doses. Contracts with manufacturers should be timely enough in order to allow availability of the vaccine stockpile by January 2016, as per ICG recommendation.

- To inform about the risk and warn neighbouring countries, Niger should finalize and disseminate the report on fake vaccine use.

4.2. Treatment and chemoprophylaxis

The recommended policy of treating cases of suspected bacterial meningitis with a five day course of ceftriaxone should be maintained as far as possible during epidemics. Ambulatory treatment in health centres with referral to hospital for more severe cases should be presented as a valuable option to countries.

In some situations such as large-scale epidemics, in very remote areas or if weak infrastructure, in confirmed meningococcal meningitis epidemics, single-dose ceftriaxone treatment protocols may be implemented. Review after 24 hours and, if not improved, a switch to 5 day ceftriaxone treatment is recommended(3).

Given the uncertain availability of sufficient quantity of C vaccines and the potential for prevention of cases through single dose oral ciprofloxacin to household members of cases, a randomized trial of this intervention is recommended (G. Alcoba, J. Stuart).

4.3. Surveillance

Enhanced surveillance should be maintained in all countries of the meningitis belt. Case based surveillance is complementary to enhanced surveillance and should be adapted during epidemics. Improvements in national surveillance capacity should be supported by WHO coordinated partner missions and by MenAfriNet. Preparedness should be reinforced in all countries, with particular emphasis on higher risk areas. These are believed to be: epidemic areas in Niger and Nigeria, which were partially vaccinated in 2015; newly affected areas at the end of the 2015 epidemic season in Niger and Nigeria; neighbouring countries, in particular those were NmC has been detected (Benin, Burkina Faso, Côte d'Ivoire and Mali).

To improve preparedness for epidemics:

- Standardised tools through MenAfriNet and SOPs through WHO-AFRO should be made available to countries before January 2016.
- Results of laboratory confirmation should be available rapidly in country to support treatment and vaccination policy decisions.
- Lumbar puncture kits, rapid diagnostic tests and laboratory reagents should be pre-positioned.
- Transport media should be pre-positioned, with clear instructions on their use.
- Agreement for rapid transfer of samples to WHO collaborating centres should be made as soon as possible.

Action is needed by WHO on the following:

- Strategy and criteria for deployment of mobile laboratories.
- Transfer of CSF samples from countries to WHO collaborating centres.
- Specification for manufacture of RDTs (Product Target Profile) .

5. Research

Areas suggested for further research:

- development and evaluation of RDTs under field conditions , including testing of Institut Pasteur's prototype cassette in volunteer countries.
- cluster randomized trial of chemoprophylaxis to household contacts of cases (protocols should be prepared now and pre-approval should be obtained from ethical review boards in more than one country)
- carriage studies of vaccine impact
- impact of ACYW conjugate vaccine (Ouallam, Niger)
- modelling of NmC and replacement
- environmental factors in prediction of disease
- seroprevalence, population immunity to NmC
- *N. lactamica* as a possible intervention
- epidemic costing
- socio anthropologic, community KAP studies
- effect of the microbiome on carriage and disease

WHO will ensure that the research areas are met and that results will be disseminated.

6. Further expert group meetings and outcome dissemination

WHO will organize a similar meeting in 2016.

Outcomes of this meeting will be disseminated in the next AFRO outbreak response meeting (planned in Niger, before end 2015).

7. References

1. Funk A, Uadiale K, Kamau C, Caugant DA, Ango U, Greig J. Sequential outbreaks due to a new strain of Neisseria meningitidis serogroup C in northern Nigeria, 2013-14. PLoS currents. 2014;6.

2. Broome CV, Rugh MA, Yada AA, Giat L, Giat H, Zeltner JM, et al. Epidemic group C meningococcal meningitis in Upper Volta, 1979. Bulletin of the World Health Organization. 1983;61(2):325-30.

3. Meningitis Outbreak Response in Sub-Saharan Africa: WHO Guideline. Geneva: World Health Organization 2014.; 2014.

Annex A

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Annex B

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FINAL AGENDA

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Serogroup C in the Meningitis Belt: Facing the Challenge

Room M405, WHO HQ, Geneva, 15-16 October 2015

Objectives of the meeting:

- Review experience from MenC epidemics in Nigeria and Niger
- Discuss plans for future epidemics

Thursday, October 15th – Chair: William Perea

08:30-09:00	*Arrival*	
09:00-09:15	*Introduction* • Welcome and Introduction • Purpose of the meeting and approval of agenda	
09:15-10:15	*Background* • Epidemiology of NmC in the meningitis belt • MenC outbreaks in the meningitis belt 2015 • Recent changes to outbreak control guidelines • Plans for multivalent conjugate vaccines	• Olivier Ronveaux • Clément Lingani • James Stuart • Marie-Pierre Preziosi
10:15-10:45	*Coffee*	
10:45-12:30	*Epidemiology, Challenges, Responses* • Experience from Nigeria 2013-15 • The case of Aliero (district in Nigeria) • Spatio-temporal study of NmC and response strategies to the outbreak in Niger 2015 • Vaccination responses during the outbreak in Niger • Experience with fake vaccines in Niger • Molecular characteristics of NmC in Nigeria and Niger	• Suleiman Aliyu • Kennedy Uadiale • Halima Boubacar • Ibrahim Alkassoum • Ibrahim Alkassoum • Dominique Caugant
12:30-13:30	*Lunch*	

13:30-15:30	*Epidemiology, Challenges, Responses* • Performance of the new alert and epidemic thresholds • Feasibility of 5 days ceftriaxone treatment • Clinical presentation and outcome in MenC disease • Progress in Rapid Diagnostic tests and application to NmC • Effectiveness of polysaccharide and conjugate vaccine strategies on MenC disease • Hypo-responsiveness, is it a problem?	• Caroline Trotter • Dorian Job • Matthew Coldiron • Fati Sidikou/ Muhamed Taha/ James Stuart for Jennifer Moïsi • Marc Rondy • Ray Borrow
15:30-16:00	*Coffee*	
16:00-17:00	*For debate* Emergence of NmC after MenAfriVac: Co-incidence or consequence? Anticipated risk in next epidemic seasons	• Marie-Pierre Preziosi • Dominique Caugant • Olivier Ronveaux
Friday, October 16th – Chair: Myriam Henkens		
09:00-10:00	*Discuss and finalize plans for 2016* • What should be done to improve surveillance? • Mass prophylaxis, an alternative to be seriously considered? • Availability of serogroup C containing vaccines	• Sarah Meyer • Gabriel Alcoba/ James Stuart • Alejandro Costa
10:00-10:30	*Coffee*	
10:30-11:45	*Discuss and finalize plans for 2016* Recommendations to countries and global partners on policy and research relating to Surveillance, Diagnosis, Treatment, Chemoprophylaxis, Vaccination	
11:45-12:15	*Conclusion and Next steps*	
12:15	*Close and Lunch*	