World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Serogroup C in the meningitis belt: What is next?

Report of WHO expert group meeting

Geneva, 6th September 2017

Introduction

An expert group met at WHO HQ, Geneva on 6th September 2017 (Annex A, B) to review experience from expansion of serogroup C meningococcal meningitis epidemics in Africa and to update recommendations made in October 2015

Background

Overview of epidemiology in the meningitis belt (M.Djingarey)

A continuing elevated risk of meningitis was seen across the meningitis belt with over 25,000 suspected cases reported in each of the last three years, 2015 -2017. In 2017, of 2,436 confirmed cases in Weeks 1-30, 35% were due to serogroup C *Neisseria meningitidis* (NmC), 13% were NmX, 10% NmW and 27% *Streptococcus pneumoniae*. The persisting high incidence of meningitis due to NmC was of major concern. Of special note was a NmC outbreak in Liberia, outside the meningitis belt, where 13 of 31 cases died and in which a septicaemic presentation was predominant.

Epidemic response in Nigeria and Niger

Nigeria (C. Ihekweazu)

An outbreak of meningitis due to NmC occurred in the north west of Nigeria, predominantly in Zamfara and Sokoto states. Over 14,000 suspected meningitis cases were reported in Weeks 1-23 2017, with a case fatality ratio of 8%. Of 474 confirmed cases, 80% were NmC. The maximum incidence approached 2,500 cases per week, peaking in Weeks 14-15. Approximately 2.1 million persons aged 2-29 years in Zamfara, Sokoto, Yobe and Katsina states were vaccinated with serogroup C containing vaccines, including 800,000 with a monovalent C conjugate (MCC) vaccine in 7 adjacent local government areas of Sokoto.

Emergency Operations Centres were set up at national and state level. Challenges were seen in surveillance such as timeliness of reporting, supplies of T-I media and rapid test kits, CSF collection, laboratory capacity. The application process for ICG vaccines was not simple. Surveillance and laboratory capacity improved markedly during the outbreak. MRC Gambia established PCR testing at the National Reference Laboratory. In preparation for the next meningitis season, improvements are being made in epidemic preparedness, communication, surveillance, laboratory capacity and response.

Niger (B. Baruani)

An outbreak of meningitis due mainly to NmC occurred concurrently with the Nigerian outbreak in the adjacent region of southwestern Niger, including Niamey. Of 3317 suspected cases, 1197 were confirmed of which 68% were NmC. An increasing trend in the proportion of NmX cases was seen from 0% in 2015 and 3% in 2016 to 18% in 2017.

Nearly 500,000 persons were vaccinated with AC polysaccharide (PS) vaccine, but the number of vaccines received through ICG was less than the country needed. Fake vaccines were known to be in circulation in Niamey. If the NmC epidemic continues next year, the risk of vaccine shortage appears high.

Discussion

Recognition of new strains is important for potential epidemic alert and response. The importance of high quality surveillance was emphasized, and the need for strong reporting systems, increased laboratory capacity, and availability of (i) skilled staff to collect CSF, (ii) adequate supplies to collect and transport specimens (iii) rapid diagnostic tests at local level.

Excellent cross border collaboration at the local level between Niger and Nigeria was noted.

Epidemiology and challenges

NmC dynamics (C.Trotter)

The spatial and temporal pattern of meningitis in Niger and Nigeria districts from 2013-2017 was examined to assess factors predicting risk of future outbreaks for vaccine targeting.

Districts did reach alert/ epidemic threshold more than once over the five-year period. In Nigeria, the risk of an epidemic in 2017 was seven times higher if alert threshold of 3/100,000 was reached in any of the previous four years, and nearly four times higher if the epidemic threshold had been crossed. Spatial analysis showed the epidemic expanding across adjacent districts and regions over this five year period.

The total population of all districts reaching the epidemic threshold in 2017 was 8.6 million. The population of all districts reaching epidemic threshold and any neighbouring districts reaching the alert threshold was approximately 11 million. If 70% aged under 30 years, then the population at risk for vaccine targeting would have been close to 8 million.

Predictions for meningitis are notoriously difficult. Conjugate vaccines offer better prospects for prevention by providing long term protection (direct and indirect). For NmC epidemics, preventive vaccination of districts reaching alert threshold could be a promising strategy but very high numbers of vaccine doses would be required. Numbers could be reduced, for example, by targeting specific age-groups, sub-districts.

Discussion

Further analysis was suggested comparing dynamics of NmC with NmA, on the risk after vaccination, on the risk to neighbouring districts, and at sub-district level. Sub-district analysis may be of less value in urban populations like Niamey because of population movement.

The group considered that pre-emptive mass vaccination campaigns were not currently feasible due to insufficient stock of conjugate vaccines. Models of effectiveness of different vaccine strategies for example targeting restricted age groups, specific geographical areas would be useful and could be used to advocate for increasing supplies of conjugate vaccines.

NmC carriage study Niger (A. Page)

A meningococcal carriage study was carried out in Niger in 2015 to assess NmC carriage prevalence globally and by age group, and compare the prevalence of NmC carriage after reactive vaccination with C containing PS vaccine during an outbreak (in Niamey) with that after using C containing conjugate vaccine (in Ouallam). Over 1800 persons, in an age stratified sample of households, were successfully recruited in each of the two communities. Difficulties with laboratory processing and PCR testing probably led to an underestimate of carriage prevalence. The *porA* qPCR had a low sensitivity and the *sodC* qPCR a low specificity. Nineteen NmC carriers were confirmed in total, a NmC carriage prevalence of 2% in Niamey and 0.7% in Ouallam. The point estimates were lower in Ouallam where the conjugate vaccine was used but the numbers were too small to draw any conclusion from this difference.

Discussion

There is still a need for validation of new PCR techniques against culture in carriage surveys because of the risk of cross-reactivity. Given existing evidence, studies of C conjugate vaccine effectiveness on carriage should not be given high priority especially as sample numbers required are high.

Molecular characteristics of NmC (D.Caugant, X.Wang, M.Taha)

The NmC outbreak strain in Nigeria and Niger (ST10217) is not related to other circulating strains of meningococci, probably arising as a new strain around 2009. A related strain (ST12446) has been recently found in Mali, that may be derived from ST10217.

Unrelated NmC strains, that are currently circulating, have been found in the Democratic Republic of Congo, Ethiopia, and Cameroon. The NmC cases seen in Cameroon were cc175, closely related to NmW cc175, and probably arose from capsule switching.

ST10217 has been shown to be hyperinvasive in mice. In Liberia, the NmC outbreak this year was caused by a strain closely related to ST10217 that was characterized by a high case fatality ratio and an atypical presentation including abdominal pain and purpura with septicaemia. No cases of meningitis were recognised.

Discussion

The clinical presentation seen in Liberia was similar to that recorded in some cases during the current increase of cc11 serogroup W in the UK, and was quite different from typical presentation of meningitis in the belt. Other anecdotal reports of septicaemic presentation have been noted from Niger and Nigeria, but the case fatality ratio among suspected cases was not higher than expected. Research is needed to help answer questions about recommending blood testing in addition to CSF sampling and changing the meningitis case definition to include meningococcal septicaemia. Rapid diagnostic tests (RDTS) on blood and urine should be evaluated. It was noted that target product profiles for RDTs have been developed by WHO, and that a field evaluation of meningococcal and pneumococcal dipsticks is to take place in Burkina Faso and Niger in 2018, including tests on CSF and urine.

Serological data from Niger (C. Trotter).

Nearly 400 stored serum samples collected from a population sample in Niger in 2012 were tested for serogroup C antibody levels, both IgG and serum bactericidal activity (SBA). Immunity to serogroup C meningococci in Niamey before the NmC outbreak was low, around 20% had likely protective SBA levels (rSBA≥8). Immunity was very low among those aged <15 years. Population susceptibility in Niger was greater than that in UK before the introduction of MCC vaccine in 1999.

Vaccine availability (A. Costa)

For 2017, the ICG asked for the constitution of an international stockpile of 5 million doses at the beginning of the season. This target was not met. During 2017, 2.9 million doses were released from the ICG stockpile with nearly all the vaccine stock (both PS and conjugate vaccine) being used.

The current 2018 stockpile estimate is Men ACYW PS 700,000 doses, MenACW 1.5 million (production 300,000 doses/month), ACYW conjugate 200,000, making a total of 2.4 million CW containing vaccines compared with the forecasted need of 5 million. Other potential supplies of non-prequalified C containing vaccines include 4.3 million ACYW PS and 1.8 million AC PS vaccines.

Discussions are being held with Gavi on funding more conjugate vaccines, planning for a 5-year procurement strategy and promoting development of an affordable polyvalent conjugate vaccine.

Responses

Vaccine effectiveness for NmC (M.Coldiron)

In 2017 a retrospective case control study of vaccine effectiveness was conducted in Niamey 2, part of the city that had been subject to repeated epidemics accompanied by reactive vaccination in 2015 (all 2-14-year olds), 2016 (2-14 year olds in three health districts) and 2017 (all 2-19 year olds) with AC and ACWY PS vaccines.

In 2015 a retrospective case control study in Niamey found ACW and ACWY vaccines to be 84% and 95% effective respectively. In the 2017 study, no significant protection was found from any vaccine administered in 2015-2016. Few suspect and no confirmed NmC cases were declared in 2017 post-vaccination campaign, not allowing estimation of vaccine effectiveness of the 2017 vaccination. Given the high proportion of PCR-negative cases (of 126 cases with PCR result, 101 tested negative and only 15 were confirmed NmC), it is possible that many suspected cases were not true cases of meningitis. Recall bias or loss of vaccine effectiveness are other potential explanations.

Chemoprophylaxis (M.Coldiron)

A three-arm cluster-randomized trial assessed the impact of single-dose oral ciprofloxacin for household and community contacts of meningitis cases on the incidence of meningitis during an NmC epidemic in Niger. After notification of a case, villages were randomised to receive no prophylaxis (standard care), prophylaxis to household contacts, or prophylaxis to the whole village. Preliminary analyses show villages receiving village wide prophylaxis had a marked reduction in meningitis attack rates after the intervention compared to the standard care arm, whereas attack rates in the household prophylaxis arm were similar to those in the control arm. Of the confirmed NmC cases occurring after intervention, none were seen in the village intervention arm.

Faecal carriage of ciprofloxacin-resistant enterobacteriae was very high at baseline in the study area. There was a non-significant increase in prevalence of carriage of ciprofloxacin-resistant enterobacteriae after 8 days in the village-wide prophylaxis arm.

Recommendations

The recommendations of the 2017 WHO Expert Group are set out in the table below alongside the recommendations made in 2015.

Outcome dissemination

Outcomes of this meeting were disseminated in the AFRO meeting in September 2017 and will be edited for publication in the WER.

Table 1: Recommendations of WHO Expert Group on Serogroup C meningococcal meningitis epidemics in the African meningitis belt: 2015 and 2017

WHO Expert Group Recommendations	
2015	**2017**
Risk assessment	
There is an elevated risk of continuing expansion of NmC epidemics in 2016 and future years across the meningitis belt, especially in Niger, Nigeria and neighbouring countries. Immunity to NmC across the belt is expected to be low. Re-emergence of NmC is probably due to natural evolutionary change. There is no evidence of capsule switching or serogroup replacement.	**The risk of NmC epidemics is likely to persist in Nigeria, Niger and neighbouring countries.** **There is also a risk of epidemics due to other serogroups such as NmX.** **A seroprevalence study from samples in 2012 confirmed low immunity to NmC in Niger.** **Epidemics due to NmC and other serogroups after introduction of MenAfriVac are likely due to evolutionary change. There is no evidence of capsule switching or replacement of a niche left by serogroup A, but the factors driving epidemics and emergence of new strains are not fully understood.**
Preparedness	
Preparedness should be reinforced in all countries, with particular emphasis on 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, neighboring countries, in particular those were NmC has been detected.	**Preparedness should be emphasized in all countries especially in Niger, Nigeria and other countries where hyperinvasive strains of NmC has been detected (as 2015).** **It is important to complete implementation of MenAfriVac vaccination while keeping awareness that epidemics due to other serogroups may still occur.** **Vigilance for spread of the hypervirulent NmC clone should be maintained.**

2015	2017
Surveillance	
Surveillance should be strengthened across the meningitis belt.	**The molecular evolution of the outbreak clone should be monitored. Relevant specimens should be expedited to reference laboratories for confirmation and to WHO Collaborating Centres for molecular typing**
Rapid diagnostic tests (RDTs)	
The development and validation of new RDTs should be accelerated and product specifications made available	**Further market exploration, alongside development and evaluation of RDTs should be pursued.**
Case management	
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, with case management in health centres and referral to hospital for more severe cases. In large-scale epidemics of conformed meningococcal meningitis, in very remote areas or if weak infrastructure, single-dose ceftriaxone treatment protocols may be implemented. Review after 24 hours is essential, with referral for hospital care where needed.	**No change in recommendations**
Chemoprophylaxis	
Chemoprophylaxis is not currently recommended in epidemics. A randomized trial of single dose oral ciprofloxacin to household members of cases is recommended.	**Effectiveness of village wide prophylaxis with single dose ciprofloxacin was shown in a randomised trial. These results are encouraging. Further evidence of duration of protection and risk of ciprofloxacin resistance among both meningococci and gut flora is needed before recommending a policy of village wide prophylaxis in epidemics.**

2015	2017
Vaccine supply and strategy	
High priority should be given to increasing the stockpile of C containing vaccines. Procurement should not be restricted to prequalified vaccines. Contracts with manufacturers should be timely enough in order to allow availability of the vaccine stockpile by January 2016. Previous administration of C-containing PS vaccines reduces the immune response to a subsequent dose of another C-containing PS vaccine and to a lesser extent by a C conjugate vaccine. The implications of the observed reduction in immune response are not known. It is preferable to use conjugate rather than PS vaccines but both can be used Given the limited supply of C-containing vaccines 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. Given the potential for carriage reduction after administration of conjugate vaccines, a restricted age group might be considered for vaccination with conjugate vaccines e.g. 5-15 or 2-19 years.	**The predicted vaccine stockpile for 2018 is currently too low. WHO and countries should advocate with Gavi to increase the size of the stockpile, develop a 5-year procurement strategy, reduce the cost of conjugate vaccines and expedite trials of affordable polyvalent conjugate vaccines.** **Countries could preposition stocks if affordable and accessible from manufacturers.** **Pre-emptive campaigns are not currently feasible due to insufficient stock of conjugate vaccines. Models of different vaccine strategies e.g. targeting restricted age groups and taking into account the vaccine coverage needed for herd protection, are recommended, and could be used to advocate for increasing supplies of conjugate vaccines.**
Research	
• RDT development and evaluation • Antibioprophylaxis • Carriage studies of vaccine impact • Impact of conjugate (ACYW, in Ouallam) • Modelling of NmC • Environmental prediction • NmC seroprevalence • *N. lactamica* as a possible intervention • Co-morbidity concomitant • Economical work: epidemic costing • Socio anthropologic – community KAP studies	• **Further RDT development and evaluation** • **Further evaluation of mass chemoprophylaxis** • **Models of impact and costs of different conjugate vaccine strategies** • **Investigating clinical presentation and laboratory diagnosis of septicaemia during NmC epidemics** • **Better understanding of NmC carriage during epidemics (prevalence and comparison of NmC carriage and invasive strains)** • **Epidemic costing (in progress) Community perceptions of continuing risk of epidemics and meningitis vaccines**

Annex A

List of participants

Ray Borrow, Public Health England, United Kingdom: Ray.Borrow@phe.gov.uk

Dominique Caugant, NIPH Oslo, Norway : dominique.caugant@fhi.no

Matthew Coldiron, Epicentre/ Médecins Sans Frontières (MSF), France : matthew.coldiron@epicentre.msf.org

Tanja Ducomble, MSF Geneva, Switzerland: tanja.ducomble@geneva.msf.org

LeAnne Fox, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America: lfox@cdc.gov

Chikwe Ihekweazu, Nigeria Centre for Disease Control, Abuja, Nigeria: chikwe.ihekweazu@ncdc.gov.ng

Ryan Novak, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America: bnk4@cdc.gov

Anne-Laure Page, EpiCentre/ Médecins Sans Frontières (MSF), France : anne-laure.page@epicentre.msf.org

Muhamed-Kheir Taha, Institut Pasteur, Paris, France : muhamed-kheir.taha@pasteur.fr

Caroline Trotter, University of Cambridge, United Kingdom: clt56@cam.ac.uk

Xin Wang, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America: gqe8@cdc.gov

Headquarters, Regional and Country Offices

Baruani Bienvenu, WHO WCO, Niamey, Niger: baruanigoyb@who.int

Alejandro Costa, WHO HQ, Geneva, Switzerland: costaa@who.int

Mamoudou Djingarey, WHO IHM, Brazzaville, Congo: djingareyh@who.int

Antoine Durupt, WHO HQ, Geneva, Switzerland: durupta@who.int

Katya Fernandez, WHO HQ, Geneva, Switzerland: fernandezk@who.int

William Perea, WHO HQ, Geneva, Switzerland: pereaw@who.int

Olivier Ronveaux, WHO HQ, Geneva, Switzerland: ronveauxo@who.int

James Stuart (meeting rapporteur), London School of Hygiene and Tropical Medicine, London, UK : james.stuart@lshtm.ac.uk

Alemu Wondimagegnehu, WHO CO-WR, Abuja, Nigeria: alemuwo@who.int

Anne Perrocheau, WHO HQ, Geneva, Switzerland: perrocheaua@who.int

Annex B

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AGENDA

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Serogroup C in the Meningitis Belt: What is next?

Room 405, WHO HQ, Geneva, September 6 2017

Objectives of the meeting:

- Review experience from NmC expansion in Africa
- Discuss plans for future epidemics
- Propose future research areas

Morning 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* • 2015 meeting recommendations - overview • Meningitis epidemiology in the meningitis belt, 2010-2017 (10 minutes) • Response to NmC outbreak, Nigeria, 2017 (10 minutes) • Response to NmC outbreak, Niger, 2017 (10 minutes) **Discussion**	• WHO - HQ • WHO-AFRO • Nigeria • Niger
10:15-10:45	*Coffee*	
10:45-12:15	*Epidemiology, Challenges* • Geospatial extension of the outbreak in Niger and Nigeria • NmC carriage study • Molecular characteristics of NmC Latest molecular analyses • Serological data from Menafricar carriage data • Availability of serogroup C containing vaccines (polysaccharide and conjugate) **Discussion**	• Caroline Trotter • Epicentre • NIPH Oslo / CDC /IPP • Caroline Trotter • WHO-HQ (ICG)

12:15-13:30	*Lunch*	
Afternoon chair: Ray Borrow		
13:30-14:30	*Responses* • Effectiveness of polysaccharide and conjugate vaccine strategies on NmC disease • Mass prophylaxis – preliminary results of Niger study	• Epicentre
14:30-15:30	*For debate:* • Anticipated risk in next epidemic seasons • Pre-emptive campaigns – an option? • NmC expansion and MenAfrivac: what is the message?	
15:30-16:00	*Coffee*	
16.00-17:00	*Recommendations* • to countries • to WHO • to partners	
17:00-17:15	*Conclusions and next steps*	