Meningococcal meningitis in Africa: What's happened since the MenA CV introduction and when can we expect a licensed ACYWX conjugate vaccine

Meningitis Research Foundation, British Museum
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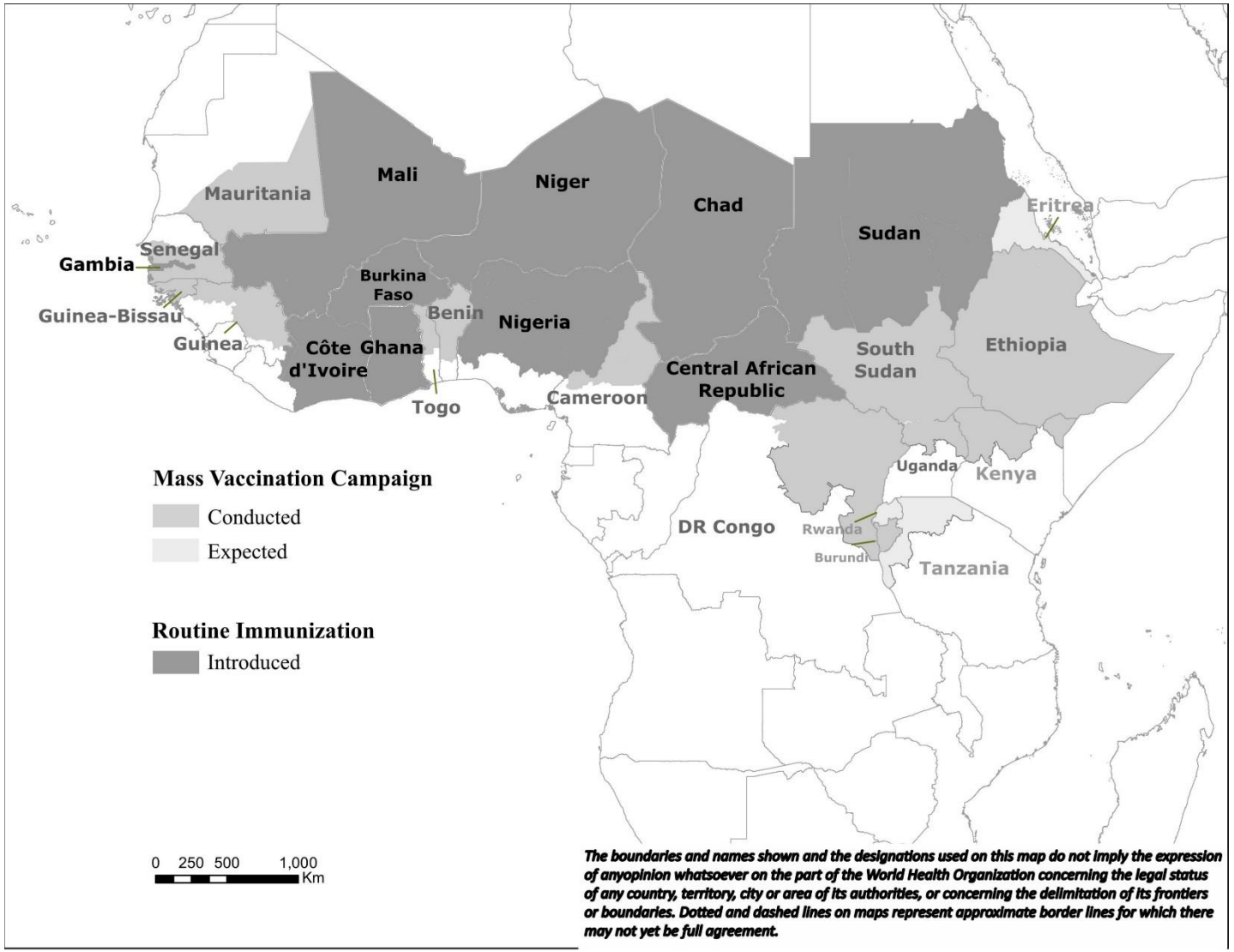
MenACV roll out as of October 2019



23 countries conducted mass campaigns

+ Eritrea planned Q4-2019

315+ million 1-29 year-olds vaccinated

Dec 2010 - July 2019

10 countries introduced into routine

+ 4 planned in 2020

10+ million children vaccinated

July 2016 - Dec 2018

No confirmed case of NmA in the meningitis belt in 2018-2019.

Ongoing efforts to sustain the impact of campaigns through routine immunization

Suspected cases of meningitis and pathogens identified since 2010 in 15 countries (WHO surveillance data)

Year	Suspect cases	Nm A	Nm C	Nm Y	Nm W	Nm X
2010	30,103	439	4	0	726	55
2011	22,000	197	5	1	513	154
2012	28,805	88	4	1	1,009	138
2013	19,685	22	10	0	237	15
2014	21,641	5	48	1	286	11
2015	27,304	80*	1,224	0	545	20
2016	26,029	22*	375	6	719	68
2017	34103	2	891	2	263	333
2018	20,843	0	466	0	71	293
2019 (wk 26)	13,120	0	317	0	96	102

*Cases not confirmed

Epidémies de méningite 2019

countries	Suspected cases (2019)	Deaths (2019)
Burkina Faso	1 695	125 (CFR = 7.4%)
Chad	336	49 (CFR = 14.6%)
Togo	213	7 (CFR = 3.3 %)
Ghana	746	20 (CFR = 2.7%)

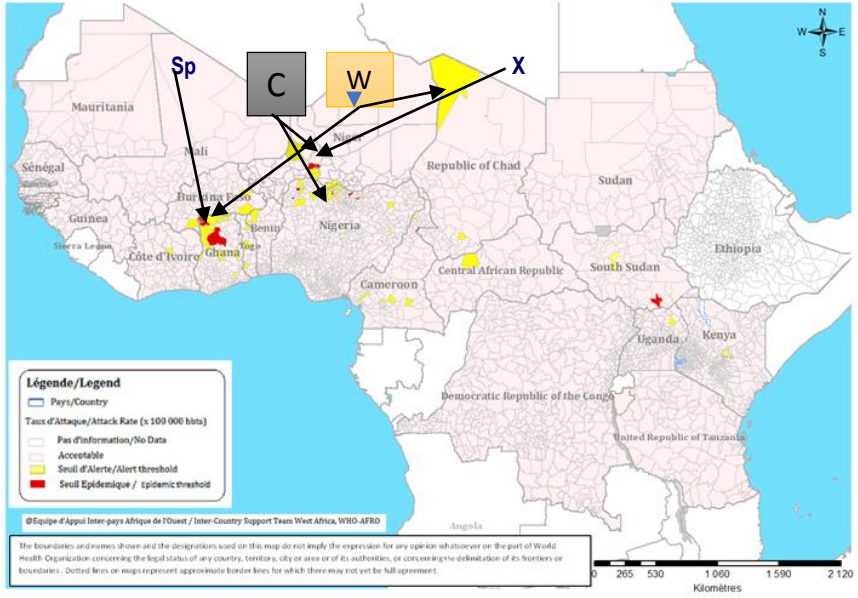


Figure A : Recapitulative map of cumulative Meningitis attack rates : epidemic season 2018 w 1-26

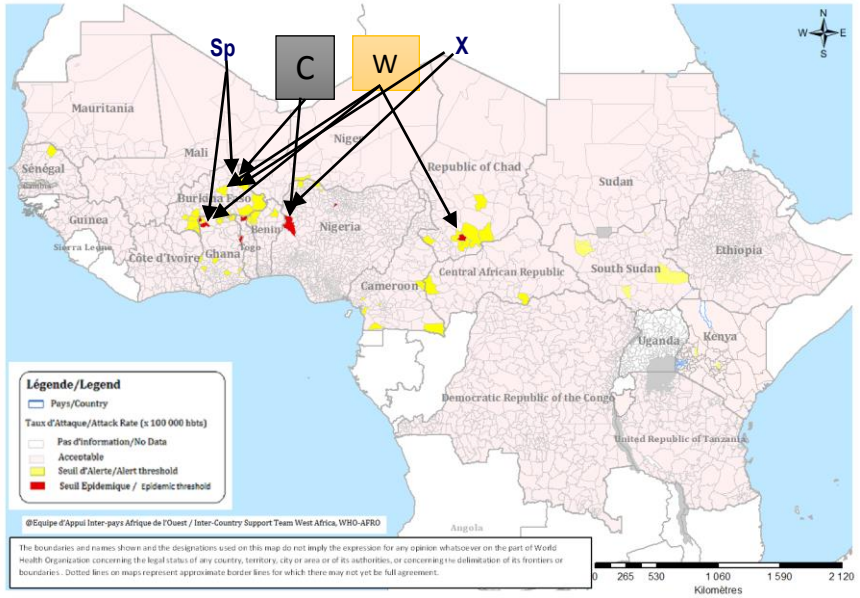
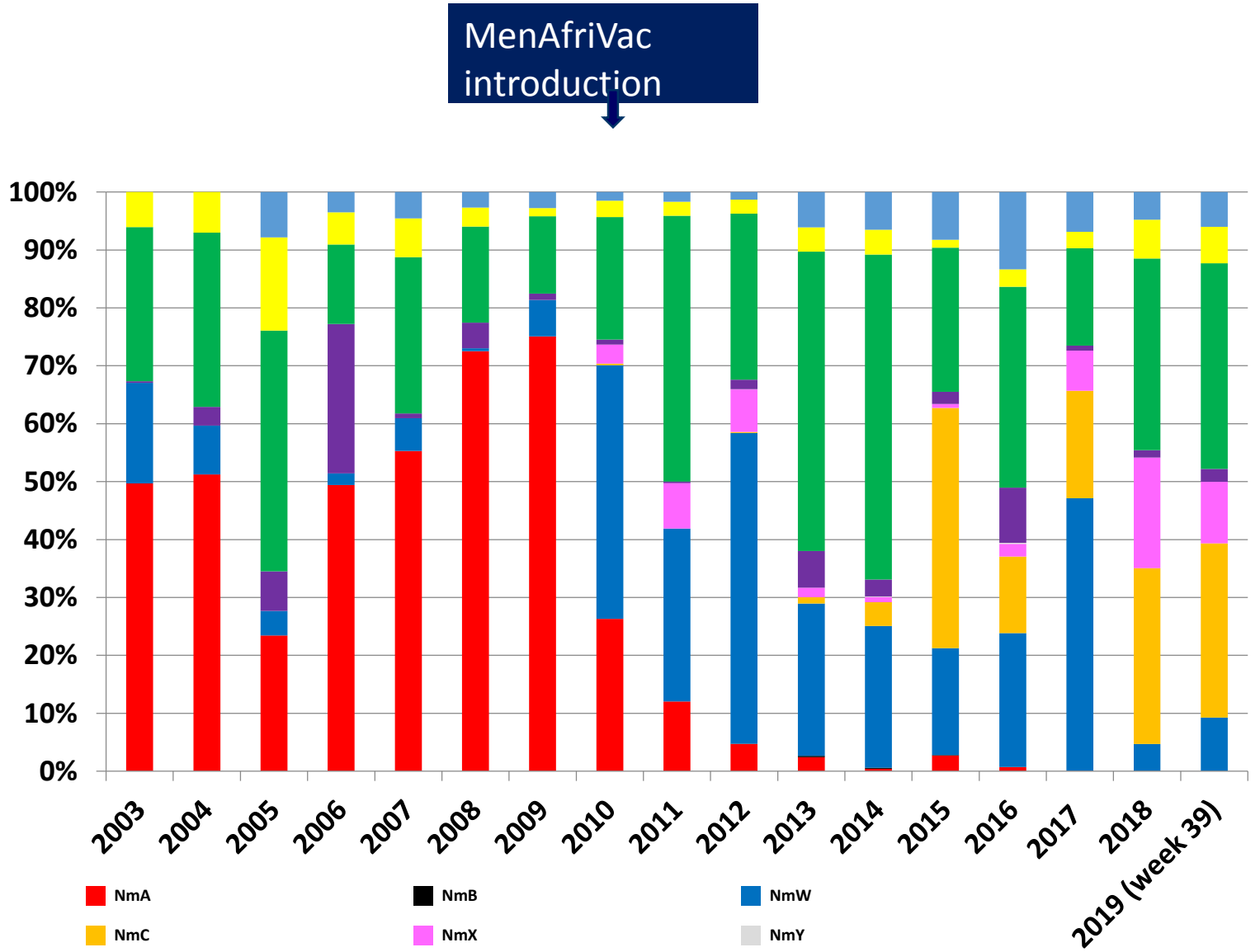


Figure B : Recapitulative map of cumulative Meningitis attack rates : epidemic season 2019 w 1-26

Fractional distribution of African CSF isolates 2003-2019



2019

Distribution of CSF isolates

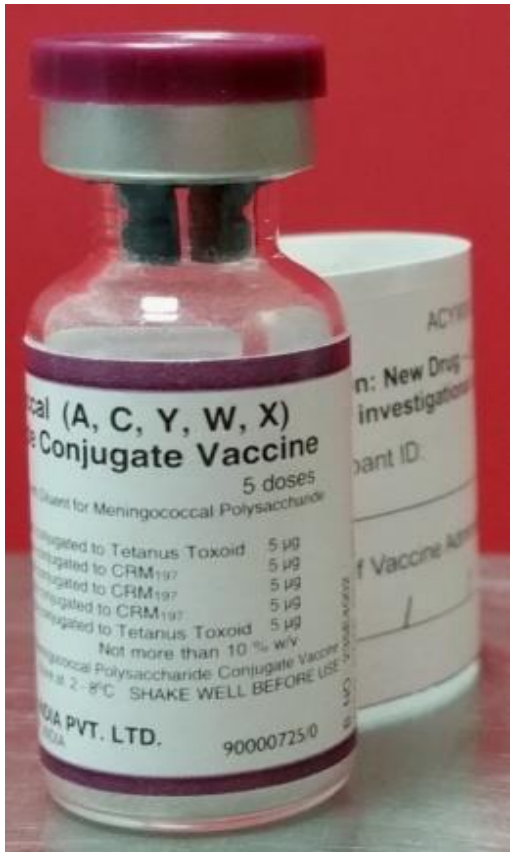
Sp	(36%)
NmC	(30%)
NmX	(11%)
NmW	(9%)
Hib	(6%)
NmA	(0%)

Problem Statement

- Outbreaks due to serogroups C, W and X still occur, and have compelled reactive vaccination campaigns through the ICG system using polysaccharide and conjugate vaccines.
    - Licensed quadrivalent conjugate vaccines are expensive and don’t cover serogroup X disease.
    - Despite reactive deployment of polysaccharide vaccines, many cases still occur and lives are lost to a vaccine-preventable disease.
    - Market incentives are lacking for suppliers of PS vaccines for the stockpile and current ICG stocks are insufficient.
- Proactive disease control is preferable if it is affordable.

Goal:

To eliminate epidemic meningitis from sub-Saharan Africa through the development, testing, licensure, and introduction of a pentavalent (A, C, W, X, Y), heat-stable meningococcal conjugate vaccine.



NmCV-5 Composition

Composition	Qty
Men A PS-TT	5 µg/ Dose
Men C PS-CRM	5 µg/ Dose
Men Y PS-CRM	5 µg/ Dose
Men W PS-CRM	5 µg/ Dose
Men X PS-TT	5 µg/ Dose
Sucrose	15 mg/vial
Sodium citrate	2.5 mg/vial
Tris buffer	0.61 mg/vial

Diluent	Sodium chloride in WFI (0.9% w/v)
Preservative	None*

Vaccine Presentations : Single Dose, 5 Dose

* WHO PSPQ recommendation in place

Overview of NmCV-5 clinical development plan

Phase (Study site)	Population	Primary objective	Status
Phase 1 (US)	18-45 years	Safety	Completed
Phase 2 (Africa)	12-16 months	Safety	Completed
Phase 3 (Africa)	2-29 years	Immunogenicity	Ongoing
Phase 3 (India)	18-85 years	Immunogenicity Lot-to-lot consistency	Planned
Phase 3 (Africa)	9-15 months	Immunogenicity Non-interference with EPI vaccines	Planned

Phase 1 study design and results

- Double-blind, randomized, controlled study conducted at CVD, Baltimore.
- 60 adults (18-45 years) randomized to receive single IM dose of adjuvanted NmCV-5, non adjuvanted NmCV-5 or Menactra.
- Solicited reactions (until day 7), and unsolicited AEs (until day 28) including SAEs (throughput the study period of 168 days).
- Baseline and day 28 post vaccination bleeds for rSBA test (PHE, Manchester).

Study results

- All solicited reactions were either mild or moderate, and all of them resolved without sequelae.
- No related AEs in the NmCV-5 groups; no SAE reported during the study.
- Both the formulations of NmCV-5 showed similar and numerically higher GMTs for all five serogroups relative to Menactra.

Phase 1 - Day 28 rSBA GMTs

Serogroup	NmCV-5 No adj. (N=20)		NmCV-5 +AlPO4 (N=20)		Menactra (N=20)	
	Pre	28 Days Post	Pre	28 Days Post	Pre	28 Days Post
A	**350** (119-1025)	**5595** (3324-9418)	**187** (50-708)	**6889** (3767-12596)	**33** (8.4-130)	**3214** (1978-5222)
C	**4.3** (2.0-9.2)	**6208** (3579-10771)	**9.8** (3.8-26)	**4096** (1720-9756)	**68** (40-116)	**410** (325-518)
W	**27** (6.2-117)	**11191** (6720-18635)	**8.0** (2.4-26)	**8192** (3439-19513)	**14** (4.2-47)	**1261** (388-4091)
X	**5.3** (1.9-15)	**1607** (892-2895)	**6.3** (2.4-16)	**1351** (577-3165)	**3.4** (1.8-6.4)	**3.1** (1.7-5.7)
Y	**24** (6.2-95)	**9410** (4935-17942)	**10** (3.0-34)	**4545** (1700-12149)	**54** (14-204)	**2353** (1302-4251)

- NmCV-5 elicited similar or somewhat better responses compared to Menactra for serogroups A, C, W and Y
- NmCV-5 elicited superior immune responses for Men X
- Adjuvanted and non-adjuvanted formulations of NmCV-5 were similar

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Phase 2 study – African Toddlers

- Observer-blind, randomized, controlled study among toddlers aged 12-16 months at CVD, Bamako, Mali (routine MenAfriVac at 9 months not given).

- 375 toddlers randomized 2:2:1 to adjuvanted NmCV-5, non adjuvanted NmCV-5 or Menactra; 2 doses three months apart.

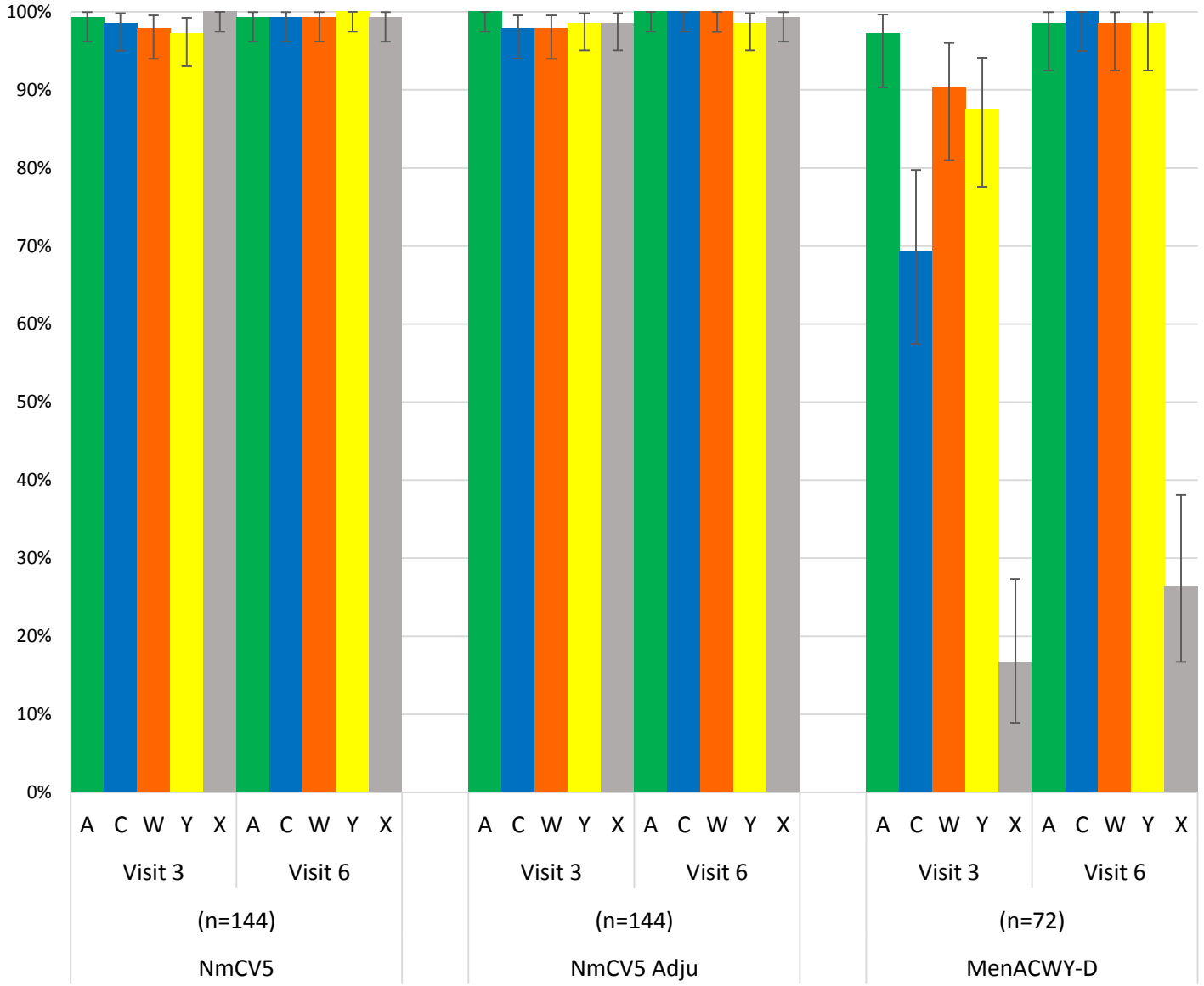
- Solicited reactions (until day 7), and unsolicited AEs (until day 28) after each dose, SAEs (throughout the study period of 84 days).

- Blood samples at baseline and day 28 post each vaccine dose for rSBA assessment.

Phase 2 study – Safety Results

- No participants reported any SAEs within 7 days of each vaccination.
- After the first vaccination the local and systemic solicited AEs ranged between 0.7% to 5.4% among all 3 groups.
- After the second vaccination there were few systemic solicited AEs.
- The majority of solicited adverse reactions were mild and all resolved uneventfully.
- There were three deaths during the study, one in each in group; none were deemed to be caused by the study products.

Proportion with 4-fold seroresponse in rSBA Titer with respect to Baseline - ACYWX-02, Toddlers, Mali



Phase 2 toddlers (Mali): % of subjects with rSBA ≥128 post dose 1

Serogroup	Non-adjuvanted NmCV-5 (N=147) (%) 95% CI	Adjuvanted NmCV-5 (N=148) (%) 95% CI	Menactra (N=74) (%) 95% CI
A	100 (97.5, 100)	100 (97.5, 100)	98.6 (92.7, 100)
C	98.6 (95.2, 99.8)	97.3 (93.2, 99.3)	54.1 (42.1, 65.7)
W	98.6 (95.2, 99.8)	98.0 (94.2, 99.6)	90.5 (81.5, 96.1)
X	100 (97.5,100)	99.3 (96.3, 100)	20.3 (11.8, 31.2)
Y	97.3 (93.2, 99.3)	99.3 (96.3,100)	87.8 (78.2, 94.3)

Phase 2 Toddlers (Mali): rSBA GMTs

Sero-group	NmCV-5 No adj. (n=144)			NmCV-5 +AlPO4 (n=144)			Menactra (n=72)		
	Post Dose 1	Pre Dose 2	Post Dose 2	Post Dose 1	Pre Dose 2	Post Dose 2	Post Dose 1	Pre Dose 2	Post Dose 2
A	**7732** (6462-9252)	**4687** (3920-5604)	**6226** (5435-7132)	**7369** (6211-8743)	**4488** (3601-5595)	**6167** (5375-7074)	**3866** (1978-5222)	**2787** (2003-3877)	**4871** (3834-6189)
C	**1144** (929-1408)	**437** (342-557)	**1367** (1174-1592)	**1095** (878-1367)	**348** (273-445)	**1393** (1201-1617)	**68** (40-116)	**30** (19-47)	**410** (325-518)
W	**6533** (4868-8768)	**2556** (1840-3550)	**8036** (6256-10323)	**5363** (3928-7323)	**2223** (1674-2952)	**7056** (5622-8857)	**1128** (615-2068)	**483** (243-961)	**2483** (1567-3933)
X	**7548** (6443-8843)	**3511** (2935-4201)	**5363** (4523-6359)	**8153** (6718-9894)	**3113** (2553-3797)	**6287** (5515-7166)	**7** (4-13)	**7** (4-12)	**12** (6-21)
Y	**2366** (1837-3047)	**1172** (892-1539)	**3189** (2701-3766)	**3010** (2491-3638)	**1387** (1129-1703)	**3267** (2801-3810)	**677** (392-1168)	**426** (252-721)	**1194** (809-1764)

Phase 2 Immunogenicity Conclusions

- Adjuvanted and non-adjuvanted formulations of NmCV-5 show similar immune responses at all timepoints.
- Menactra sero-response rates and GMTs are significantly improved following the 2nd dose.
- Some waning of immune responses is observed at 3 months post dose 1 with all groups.
- All subjects elicit high rSBA responses to the serogroups contained in the study vaccines after 2 doses.
- A single dose of NmCV-5 is better than 2 doses of Menactra for A, C, W and Y at 12-16 months of age.

Phase 3 study (2-29 YOs Africa)

- Observer-blind, randomized, controlled study among healthy individuals at 2 sites: CVD Mali and MRC The Gambia; start August 2019.
- Total follow up – 168 days post vaccination.
- 1800 subjects to be randomized as below:

Age Group	Number of Subjects		Vaccine
18-29 years	600	400	NmCV-5
		200	Menactra®
11-17 years	600	400	NmCV-5
		200	Menactra®
2-10 years	600	400	NmCV-5
		200	Menactra®

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Phase 3 study (2-29 YOs Africa)

- Primary objectives:
  - Demonstrate NI of rSBA seroresponse* or GMTs to serogroups A, C, Y, and W of NmCV-5 compared to Menactra®
  - Demonstrate NI of rSBA seroresponse* or GMTs to serogroup X of NmCV-5 to the lowest immune response of Menactra®

* - Seroresponse is four fold rise in rSBA from baseline; NI margin – 10 % for seroresponse and GMT ratio – 0.5.

- Secondary Objectives:
  - To assess safety (Solicited reactions until Day 7, unsolicited AEs until Day 28, and SAEs until Day 168)
  - To assess other immune responses

(rSBA testing will be done at NeoMed Labs, Montreal, Canada)

Phase 3 study (18-85 y/o India)

- Observer-blind, randomized, controlled study among healthy individuals
- Total follow up – 168 days post vaccination
- Multiple sites across India; study start - October 2019.
- 1640 subjects will be randomized as below:

Age group	NmCV-5			Comparator (Menactra)
18-29 years	**Lot 1**	**Lot 2**	**Lot 3**	360
	360	360	360	
30-60 years	75			25
61 – 85 years	75			25

Phase 3 study (18-85 YOs India)

- Primary objectives:
  - Demonstrate lot-to-lot consistency (GMT ratios between 0.5 to 2.0) of 3 NmCV-5 lots.
  - Demonstrate non-inferiority (NI) of rSBA seroresponse * or GMTs to serogroups A, C, Y, & W for NmCV-5 compared to Menactra®.
  - Demonstrate NI of rSBA seroresponse* or GMTs to serogroup X of NmCV-5 to the lowest immune response among four serogroups of Menactra.

* - Seroresponse is four fold rise in rSBA from baseline; NI margin – 10 % for seroresponse & GMT ratio – 0.5.

- Secondary Objectives:
  - To assess the safety (Solicited reactions until Day 7, unsolicited AEs until Day 28, and SAEs until Day 168)
  - To assess other immune responses

(rSBA testing will be done at NeoMed Labs, Montreal, Canada)

Phase 3 study (Infants, Africa)

- To be conducted among 9 month olds at 2 sites: Niger and Mali.
- Total follow up – 168 days post vaccination.
- 1200 subjects will be randomized as below:

Cohort	9 months	15 months
1 (n=400)	*NmCV-5 + MR + YF*	*DTP-Hib + Measles*
2 (n=400)	*DTP-Hib + MR + YF*	*NmCV-5 + Measles*
3 (n=400)	*DTP-Hib + MR + YF*	*Nimenrix + Measles*

- All study vaccines (NmCV-5 and Nimenrix) will be given as a single intramuscular dose

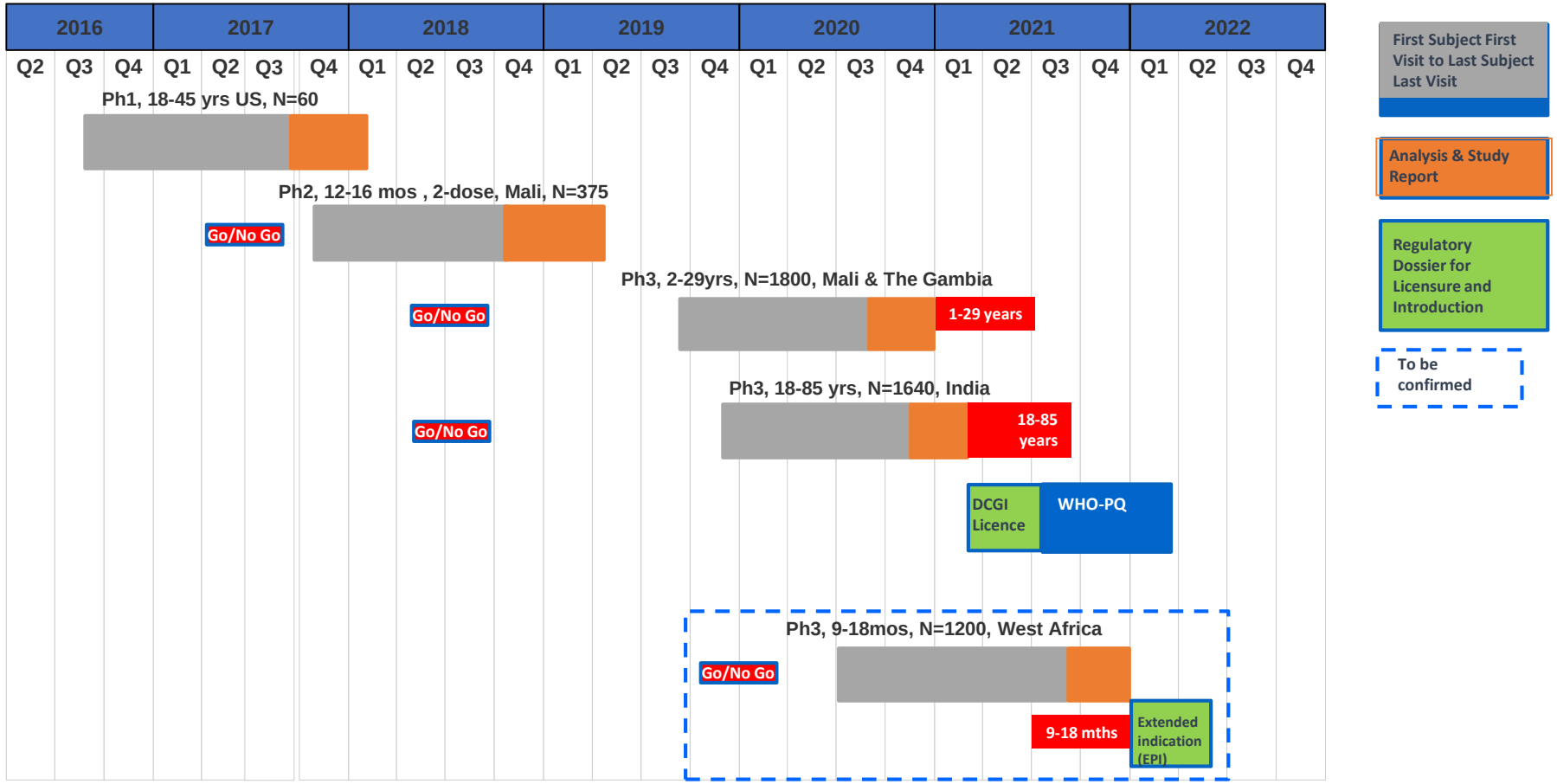
Phase 3 study (Infants, Africa)

- Primary objectives:
  - Demonstrate NI of rSBA seroresponse* or GMTs to serogroups A, C, Y and W by a single dose of NmCV-5 compared to a single dose of Nimenrix® at 28 days.
  - Demonstrate NI of rSBA seroresponse* or GMTs to serogroup X of NmCV-5 to the lowest immune response among four serogroups of Nimenrix®.
  - Demonstrate the immunological NI of EPI vaccines (MR, YF, M) when co-administered with NmCV-5 (at 9 or 15 months) compared to their co-administration with DTPHib (at 9 months)/Nimenrix® (at 15 months).

* - Seroresponse is four fold rise in rSBA from baseline; NI margin – 10 % for seroresponse & GMT ratio – 0.5.

- Secondary Objectives:
  - To assess safety (Solicited reactions till Day 7, unsolicited AEs until Day 28, and SAEs until Day 168)
  - To assess other immune response

NmCV-5 Clinical Development Plan



- Initial WHO PQ anticipated around Q2 2022.

How might a new polyvalent meningococcal be used in meningitis belt countries?

- As a stockpile vaccine to respond to CYWX epidemics
- As an EPI antigen to broaden protection against meningococci
- As a preventive vaccine to eliminate meningococcal epidemics
- Strategies may vary based on country-specific risk

Thank you!

Meningitis vaccine strategies using an ACYWX vaccine in Africa: Effects on epidemics and costs

Vaccine strategy			*Effect on meningitis epidemics*		*Costs*			
EPI vaccine (routine)	*Catch up campaigns*	*Stockpile ACYWX CV (reactive campaigns)*	*Men A*	*Non A (CYWX)*	*Case mgmt. costs*	*Vaccine purchases*	*Reactive camp. costs*	*Surveillance costs*
MenA CV	Finished	Yes	No epidemics	Non A epidemics continue	Yes	Birth cohort	Yes	Yes
ACYWX CV	No	Yes	No epidemics	Non A epidemics continue but may decr. in 10-15 years	Yes	Birth cohort	Yes	Yes
ACYWX CV	Yes (1-18 year olds)	Not necessary	No epidemics	Non A epidemics cease	None	Birth cohort & catch-up (1-18 yrs.)	None	Yes