Results from clinical trials in infants and young children safety in pregnancy and review of routine coverage data

Dr. Abraham Hodgson, Director Research and Development, Ghana Health Service

on behalf of the Meningitis Vaccine Project (MVP) & Partners

Meningococcal A conjugate vaccine impact and routine immunization schedule in infants and young children
Session 6 - Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
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Vaccine Program Rationale

- MenAfriVac, a meningococcal group A conjugate vaccine developed for the African meningitis belt *(Serum Institute of India / Meningitis Vaccine Project)*
  - PsA-TT, 10 µg/dose
  - 2009, DCG(India) marketing authorization
  - 2010, WHO prequalification
  - *mass vaccination campaigns (1 to 29 year-olds)*

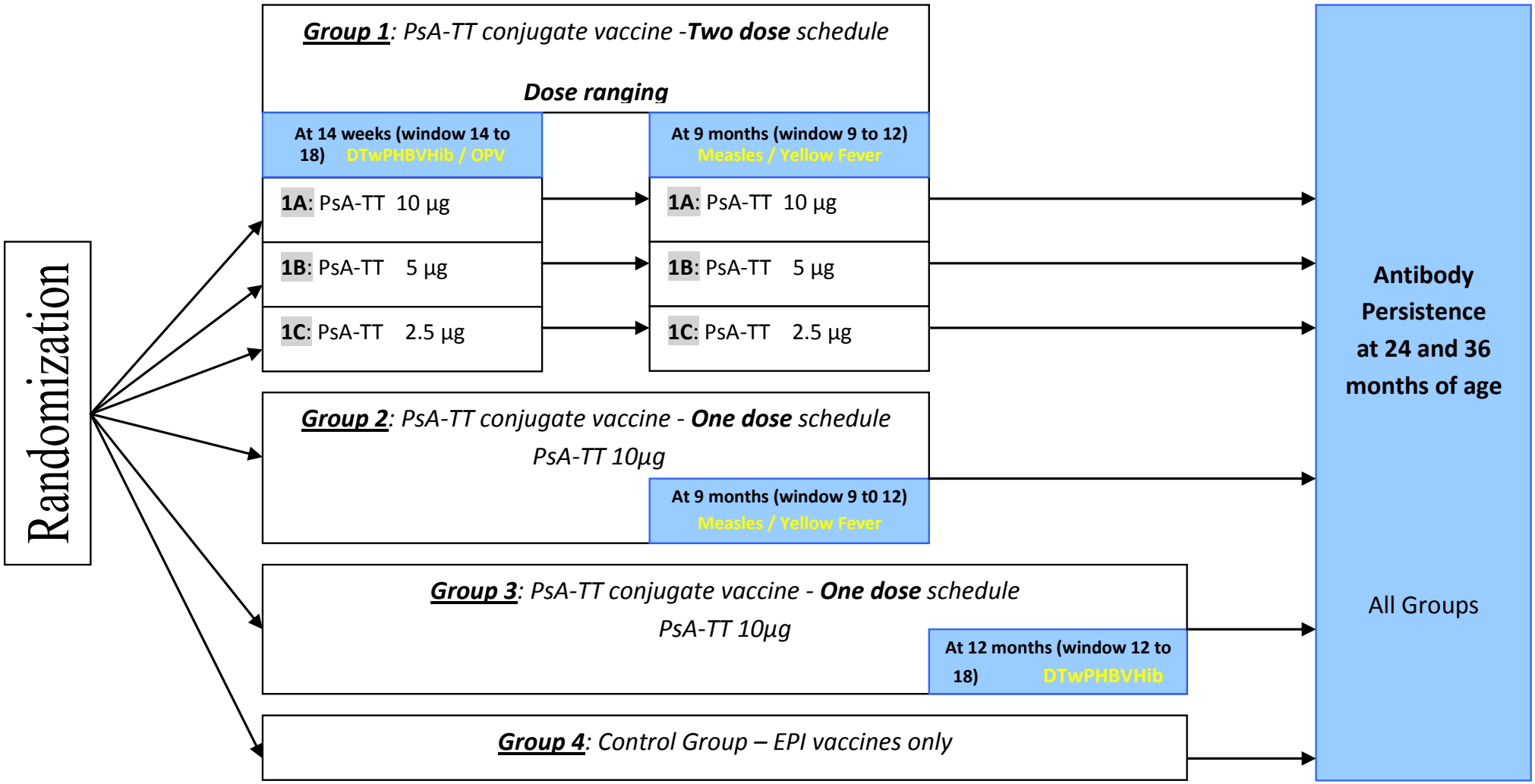
- Sustainable strategy to maintain population immunity following the initial mass vaccination campaigns ?
  - periodic follow-up campaigns of new birth cohorts
  - routine EPI immunization (dosage ? schedule ? concomitant vaccines ?)

  - ***MenAfriVac 5 µg****, license variation (3 to 24 month-olds) based on two infant studies conducted in Ghana (PsA-TT-004) and in Mali (PsA-TT-007)*

Study PsA-TT-004

Ghana, 1200 infants, primary immunization at 14 weeks of age, 11/2008-05/2012

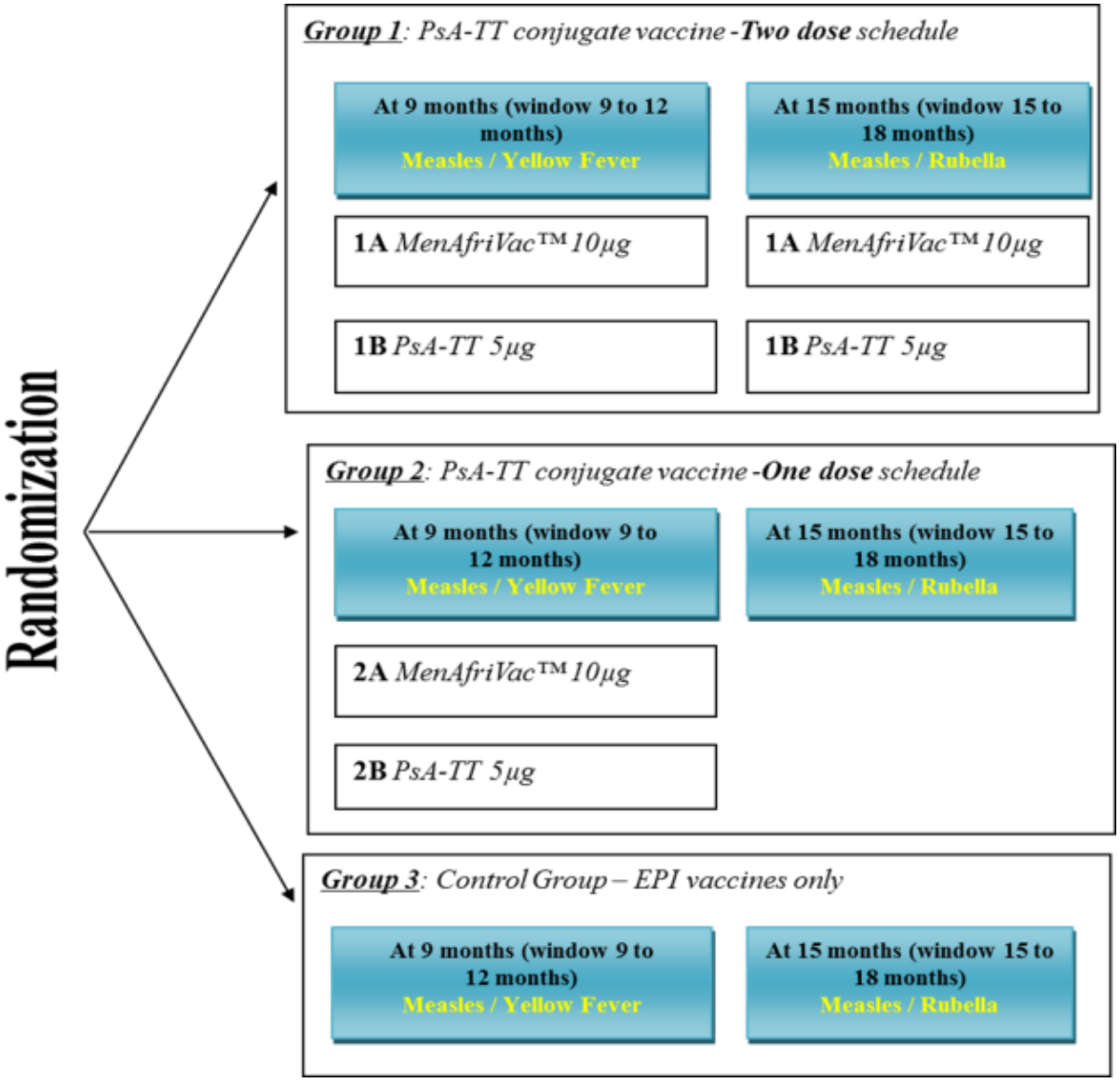
Dose-ranging, schedule response, co-administration and immune persistence



Study PsA-TT-007

Mali , 1500 infants, primary immunization at 9 months of age, 03/2012-09/2013

Confirmation of schedule and formulation, co-administration and safety



Primary immunogenicity endpoint

Ghana, PsA-TT-004 - Percentage of subjects with a ≥ 4-fold response in MenA rSBA titer with respect to baseline 28 days after each dose of PsA-TT vaccine (PP population)

No of doses of PsA-TT	Vaccine Group, dosage	28 days after a dose of PsA-TT given to Group 1 at 14 weeks of age		28 days after a dose of PsA-TT given to Groups 1 and 2 at 9 months of age	
		≥4-fold response in Men A rSBA titers % (95% CI)	Primary non-inferiority analysis difference Δ %group 1A - other groups (97.5% CI)	≥4-fold response in Men A rSBA titers % (95% CI)	Primary non-inferiority analysis difference Δ %group 1A - other groups (97.5% CI)
Two	Group 1A, 10µg	93.9 (89.3, 96.9)	----	99.4 (96.8, 100)	-----
	Group 1B, 5µg	94.1 (89.7, 97.0)	-0.2 (-6.3, 5.7)	99.4 (96.8, 100)	-0.0 (-3.4, 3.3)
	Group 1C, 2.5µg	96.7 (93.0, 98.8)	-2.9 (-8.6, 2.4)	99.4 (96.9, 100)	-0.0 (-3.4, 3.2)
One	Group 2, 10µg	2.2 (0.6, 5.6)		98.8 (95.8, 99.9)	

Non-inferiority of 5 µg and 2.5 µg vaccines to MenAfriVac demonstrated

- after 1st dose given at 14 weeks of age and
- after 2nd dose given at 9 months of age

Primary immunogenicity endpoints

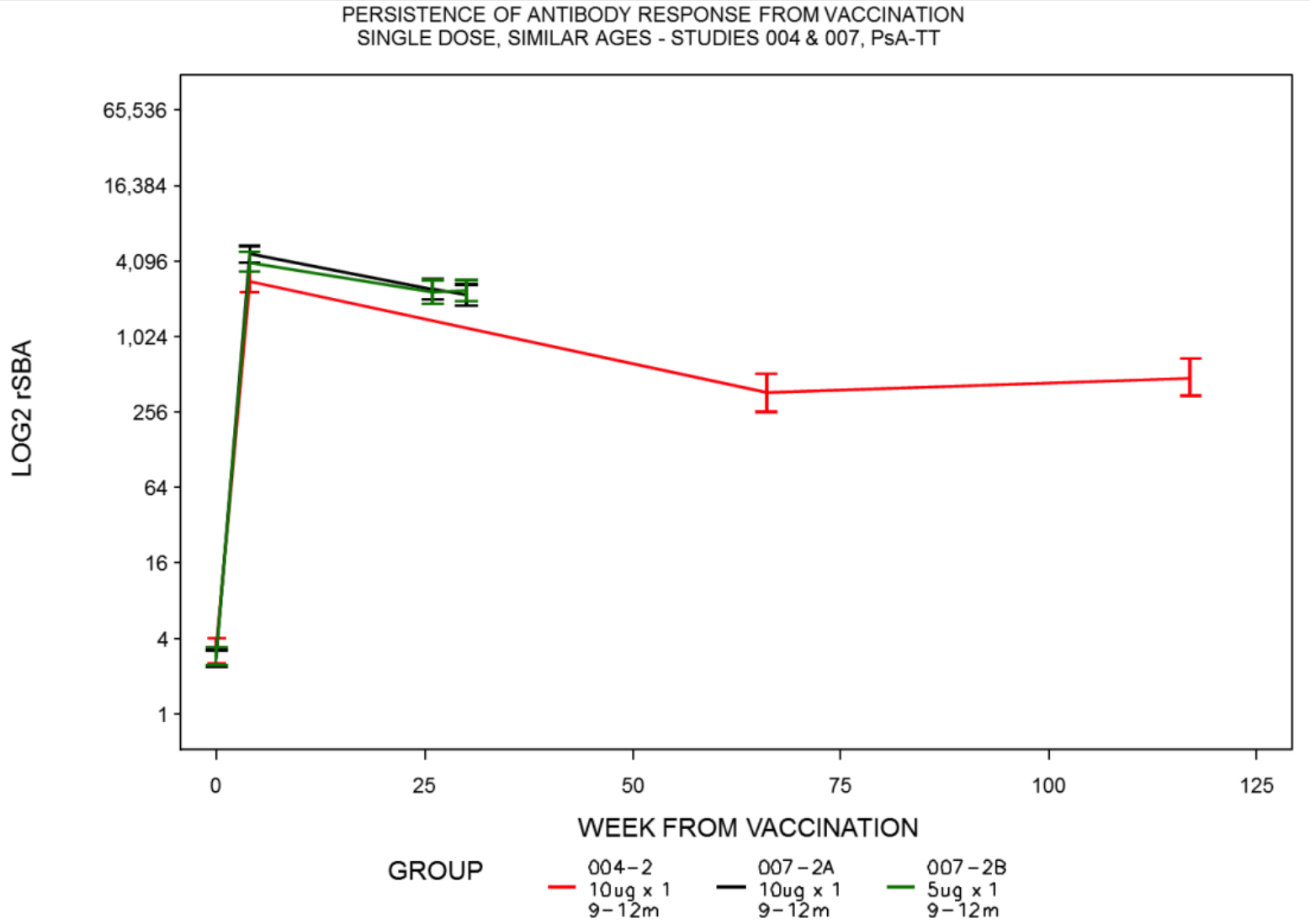
Mali, PsA-TT-007 - Percentage of subjects with a ≥ 4-fold response in MenA rSBA titer with respect to baseline and geometric mean titer (GMT) for MenA rSBA titers 28 days after the last dose of PsA-TT vaccine (PP population)

No of doses	Vaccine Group, dosage	≥4-fold response in Men A rSBA titers % (95%CI)	Primary non-inferiority analysis difference Δ %group 1A - other groups (98.3% CI)	Geometric mean titer (GMT) for MenA rSBA titers (95% CI)	Primary non-inferiority analysis ratio of GMTs of group 1A *vs.* other groups (98.3% CI)
Two	Group 1A, 10µg	100.0 (98.9, 100.0)	--	12108.3 (10960.6, 13376.2)	--
	Group 1B, 5µg	99.6 (97.9, 100.0)	0.4 (-1.8, 2.8)	11095.9 (9901.4, 12434.4)	1.1 (0.9, 1.3)
One	Group 2A, 10µg	98.6 (96.4, 99.6)	1.4 (-0.8, 4.4)	4883.1 (4244.2, 5618.1)	2.5 (2.0, 3.1)
	Group 2B, 5µg	97.2 (94.5, 98.8)	2.8 (0.6, 6.3)	4167.3 (3508.2, 4950.3)	2.9 (2.3, 3.7)

- Difference in %: all schedules non inferior to the reference 2-dose MenAfriVac
- Ratio of GMTs: only 2-dose 5 µg vaccine non inferior to the reference 2-dose MenAfriVac
- GMTs remained high and not significantly different from each other 7 months after both 1-dose schedules

Immune persistence from last vaccination (1)

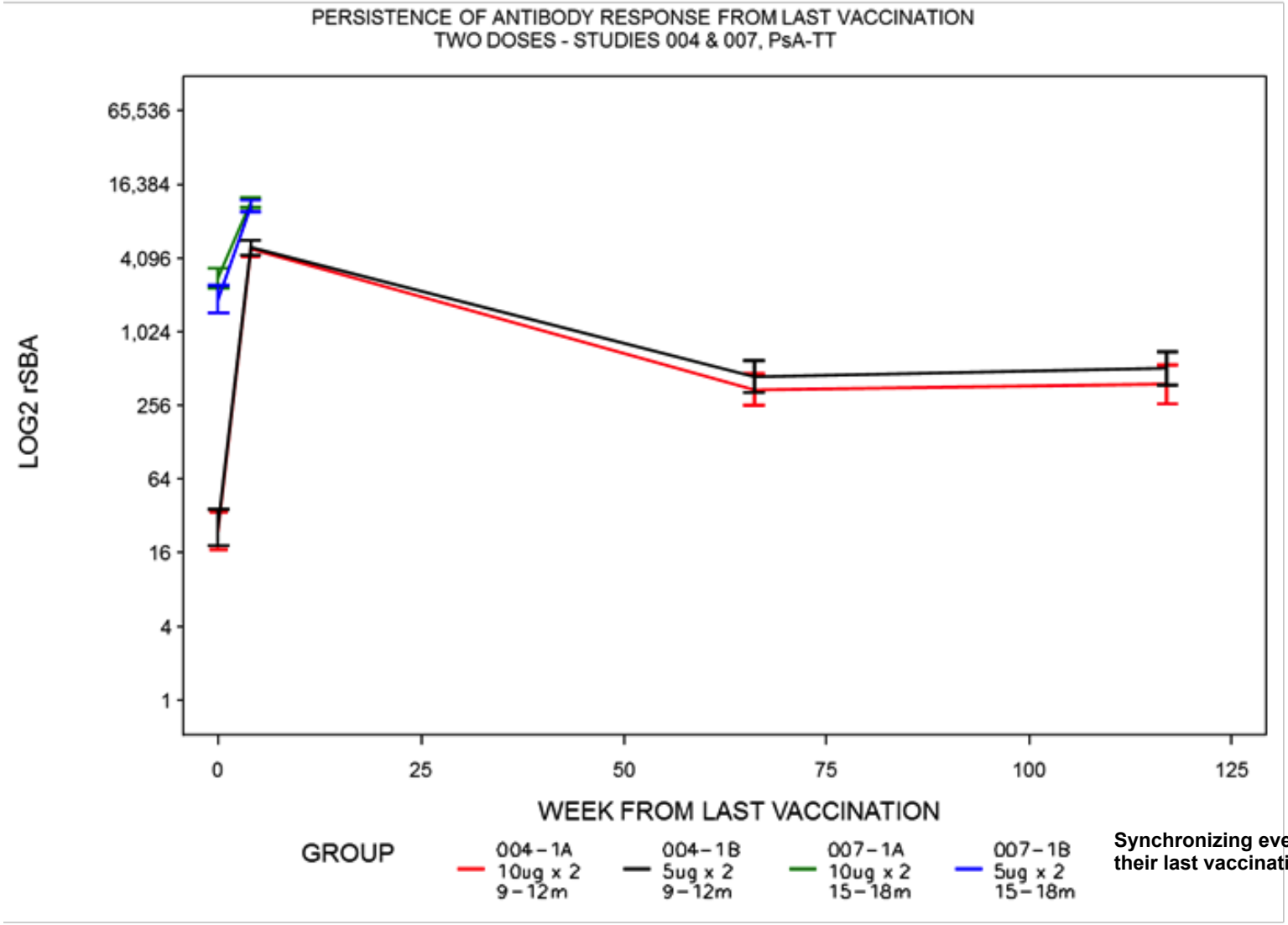
Ghana PsA-TT-004 and Mali PsA-TT-007 – Persistence of MenA rSBA response from last vaccination with 1 dose of 5µg or 10µg vaccine



Similar trajectories, rate of decline for 1 dose 5µg not significantly different from that for 1 dose 10µg

Immune persistence from last vaccination (2)

Ghana PsA-TT-004 and Mali PsA-TT-007 – Persistence of MenA rSBA response from last vaccination with 2 doses of 5µg or 10µg vaccine



Synchronizing every study subject, so their last vaccination occurs at time 0

Similar trajectories, rate of decline for 2 doses 5µg not significantly different from that for 2 doses 10µg

Immune persistence from last vaccination (3)

Ghana PsA-TT-004 and Mali PsA-TT-007 – Persistence of MenA rSBA response from last vaccination with 1 or 2 doses of 5µg or 10µg vaccine

SUMMARY CONCLUSIONS

- Induction of sustained functional immune responses
- Profile over time of 5 µg non inferior to that of MenAfriVac
- Reasonable to predict trajectory of immune response of the 5 µg vaccine will follow a similar trend

Summary of vaccine safety - Overview

Ghana PsA-TT-004 and Mali PsA-TT-007

- 3315 doses of PsA-TT vaccine administered
  - MenAfriVac 1651 doses: 1179 first and 472 second dose
  - MenAfriVac 5 µg 1270 doses: 800 first and 470 second dose
  - (and 2.5 µg PsA-TT 394 doses)
- Rates of solicited Local and Systemic Reactions, Adverse Events (AEs) and Serious Adverse Events (SAEs) similar across vaccine groups within 28 days of vaccination
  - Reactogenicity profile of PsA-TT with EPI vaccines similar to EPI vaccines alone
  - Local reactions mostly mild and transient, resolved without sequelae, observed in less than 11% of infants at the PsA-TT injection site
- Majority of AEs due to infections, consistent with background morbidity in the study areas
- All AEs unrelated to vaccines, except for 2 cases of SAEs: Facial Oedema (1 case) and Febrile Seizure (1 case)

Summary of vaccine safety - SAEs

Ghana PsA-TT-004 and Mali PsA-TT-007 - Incidence of all serious adverse events (SAEs) by system organ class or syndrome (ITT populations)

Study ID	**PsA-TT-004**						**PsA-TT-007**					
Vaccine groups	1A	1B	1C	2	3	4	1A	1B	2A	2B	3	
# subjects by arm	200	200	200	200	199	199	300	300	300	300	300	
Dosage of PsA-TT vaccine (µg)	10	5	2.5	10	10	--	10	5	10	5	--	
Primary system organ class term	***# subjects by primary system organ class***											**Total (%*)**
Infections and infestation	**56**	**43**	**46**	**51**	**51**	**49**	**8**	**4**	**3**	**7**	**9**	**327(89.8)**
Gastrointestinal disorders		1				1					1	3(0.8)
Injury poisoning and procedural complications	2	1	3	3		2		1	2		1	15(4.1)
Blood and lymphatic system disorders	7	3	2	5	3	4						24(6.6)
Congenital, familial and genetic disorders		1										1(0.3)
Metabolism and nutrition disorders					1			2		1		4(1.1)
Nervous system disorders					1							1(0.3)
General disorder	1											1(0.3)
Ear and Labyrinth Disorders					1							1(0.3)
Respiratory, thoracic and mediastinal disorders			1	1		1						3(0.8)
%of subject with at least one SAE	**31.5**	**24.5**	**24.5**	**28.5**	**26.1**	**27.6**	**2.7**	**2.3**	**1.7**	**2.7**	**3.7**	
Total # of subjects with at least one SAE	63	49	49	57	52	55	8	7	5	8	11	364

* The denominator is the total number of subjects with at least one SAE

- No difference in reported SAEs among study groups at any time during the vaccination series and follow-up observation period
- 90% cases of Infections and Infestation (primary SOC)
- 24 deaths, all unrelated to vaccines
- No specific safety signal

➢ *Continuous pharmacovigilance to assess rare events*

Co-administered vaccines - Overview

Ghana PsA-TT-004 and Mali PsA-TT-007

No adverse interaction with concomitant administration of

- Pentavalent DTwPHBVHib vaccine
  - At 14 weeks and at 12 months of age
- OPV vaccine
  - At age 14 weeks of age and at any time within < 28 days before/after (NIDs)
- Measles vaccine
  - At 9 months of age
- Yellow fever vaccine
  - At 9 months of age
- Measles and Rubella (MR) vaccine
  - At 15 months of age

No evaluation of concomitant administration with pneumococcal, rotavirus or IPV vaccines

Optimal vaccine dosage

Ghana PsA-TT-004 and Mali PsA-TT-007

PsA-TT clinical trial data from Ghana and Mali confirm

- A 5 µg PsA-containing vaccine = optimal dosage
  - Immune response non-inferior to the 10 µg PsA-containing vaccine (MenAfriVac)
  - No safety issues
  - Less TT (protein carrier) loading
  - Increased capacity of vaccine production and volume of vaccine doses
- The lowest Ag content inducing functional Ab response = optimal quality of the immune response, as experienced with other conjugate vaccines

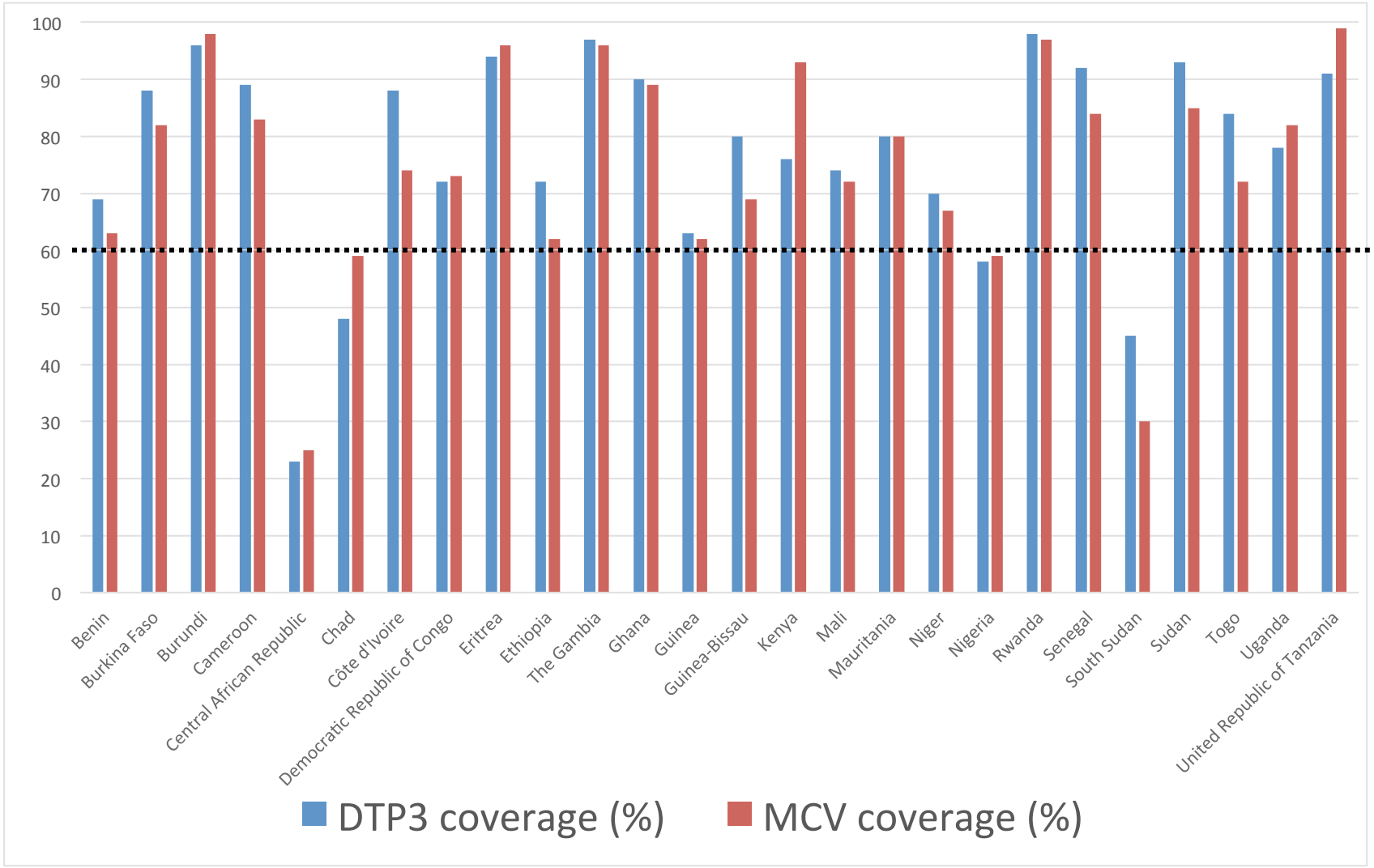
Optimal vaccination schedules

Ghana PsA-TT-004 and Mali PsA-TT-007

- The vaccine could be administered in a 1 or 2 dose-schedule, depending on age at first dose
  - 2 doses, at least three months apart, within a 3 to <9 month age-at-first-dose window or
  - a single dose from age 9 months onwards, i.e. within a 9 to 24 month age-at-first-dose window

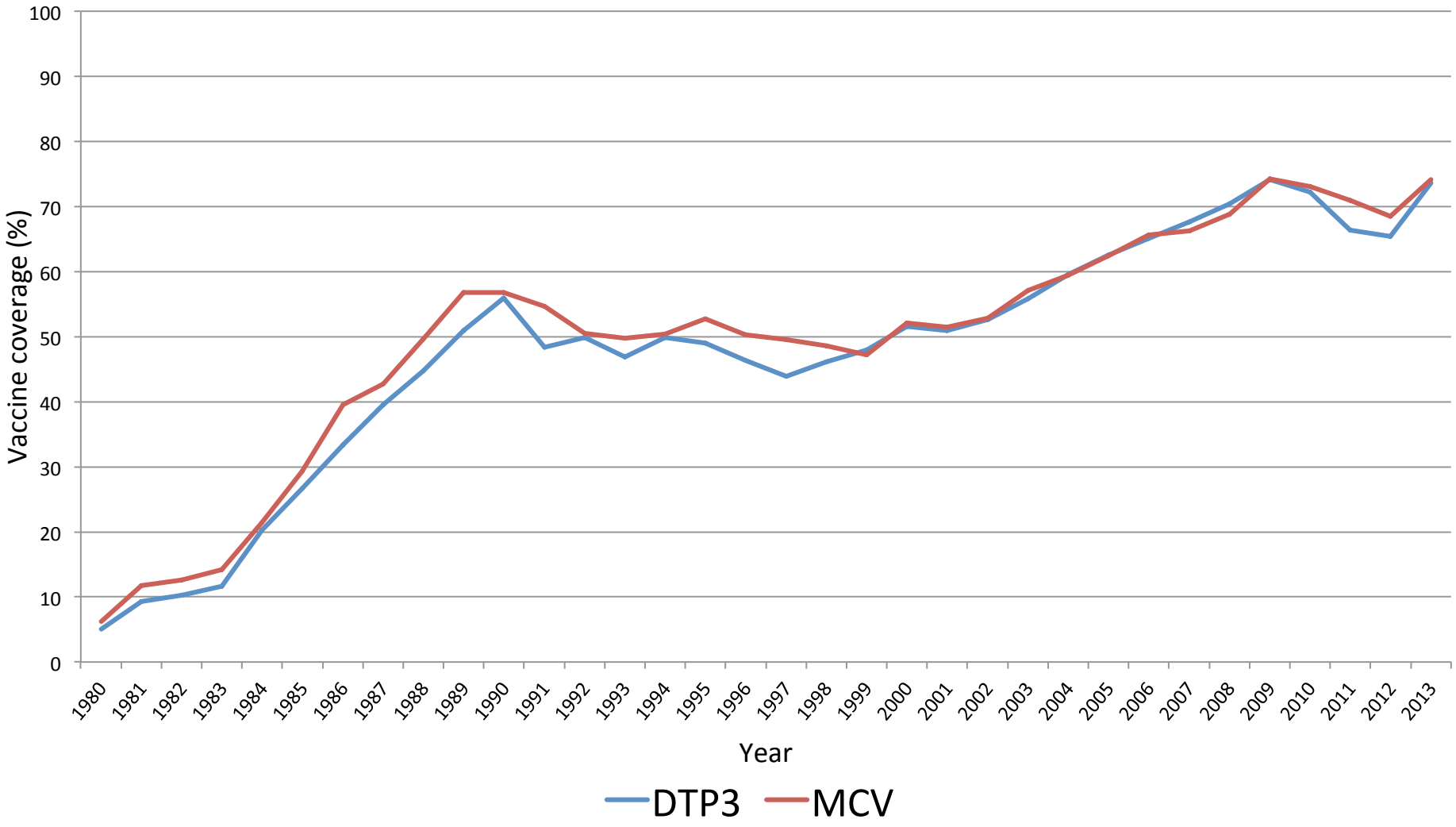
- Such schedules could fit into EPI of meningitis belt countries
  - 2-dose schedule
    - Dose 1 at age 3 months
    - Dose 2 at age 9 months / or age 15 months
  - 1-dose schedule
    - At age 9 months

EPI coverage estimates in each of the 26 countries in the meningitis belt, **2013**



Data source: WHO/UNICEF coverage estimates 2013 revision, data from 1980-2013, as of 15 July 2014

EPI annual coverage estimates in the meningitis belt (26 countries), **1980-2013**



Data source: WHO/UNICEF coverage estimates 2013 revision, data from 1980-2013, as of 15 July 2014

Next key future considerations

Policy and determination of the following components

- Optimal routine schedule(s)
  - One or two EPI doses
  - Supplemental periodic campaigns for low coverage districts
- Target population for routine
  - national or subnational
- Target population for an initial catch-up campaign
  - For cohorts missed between the initial mass campaign and the routine introduction
- Development of routine introduction plans that will
  - Promote overall enhancement of routine vaccination activities
  - Consider routine introduction of other new vaccines (e.g. IPV, PCV)

Vaccination safety in pregnancy

Global Advisory Committee on Vaccine Safety(GACVS) , June 2014

Wkly Epidemiol Rec 2014; 29: 329-31

Observational evaluation to address previous GACVS recommendations to follow up pregnant women and to monitor pregnancy outcomes

- **Navrongo Health Research Center, Northern Ghana**
  - INDEPTH network site, longitudinal demographic and health data & outcomes
  - 2 districts, total population: 156,735, 3-4 visits/yr. incl. pregnancies & outcomes
  - 9-19 Oct.2012: MenA mass campaign, 1-29 year-olds incl. pregnant women
- **Comparison of rates of pregnancy-related outcomes**
  - **in vaccinated** *vs.* unvaccinated women (who elected not to be vaccinated)
  - and *vs.* an age & season matched historical control group
- **Study results among pregnant women**
  - 1730 vaccinated, 919 not vaccinated, 3551 historical unvaccinated control group
  - No statistically significant difference in any pre-specified outcomes between vaccinated and unvaccinated women in concurrent/historical comparison groups
- **GACVS assessment**
  - Quality study and methodology, enhanced data collection in next studies
  - No concerns identified regarding vaccine use in pregnancy, neither pregnancy nor lactation are contraindications for vaccination
  - More permissive language in vaccine package insert maybe warranted