Vitamin D and Preterm Birth:
Results from a Screening and Supplementation Field Trial at MUSC

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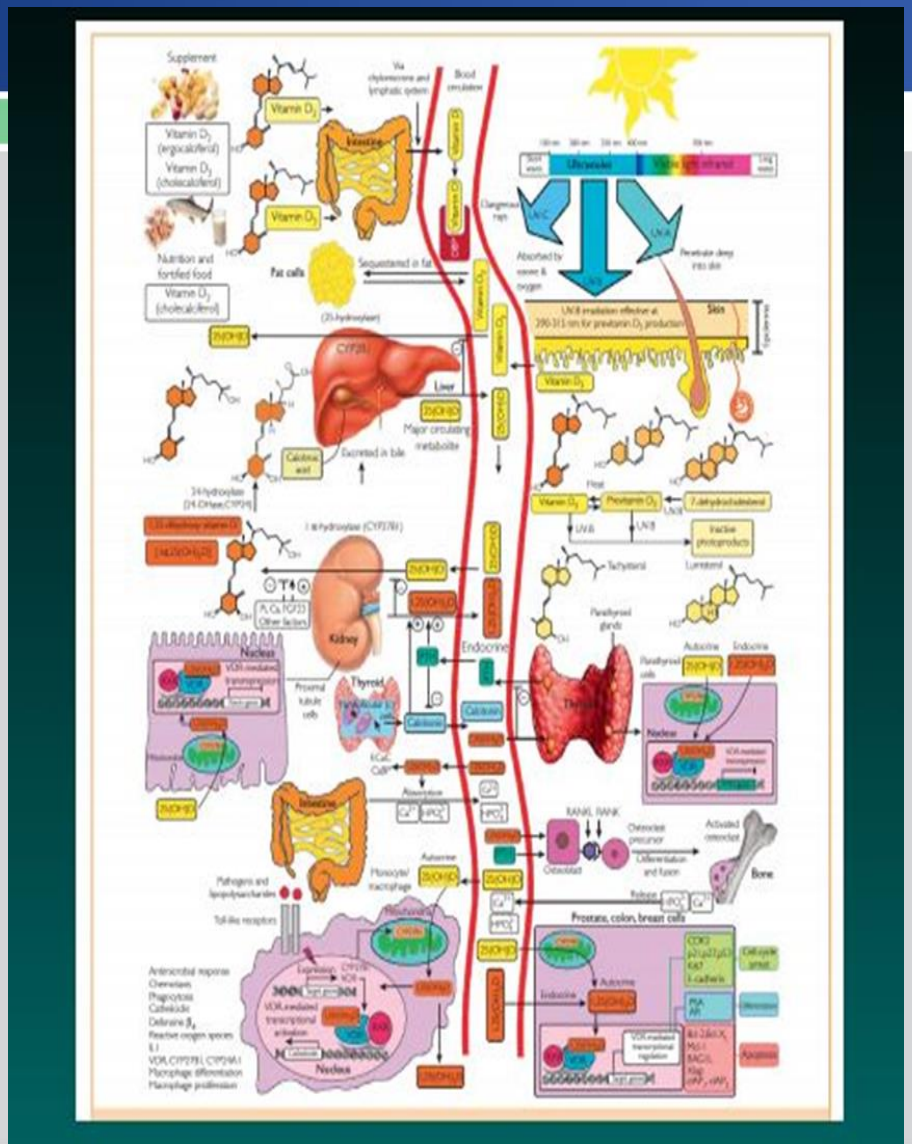
Why is Vitamin D Important?

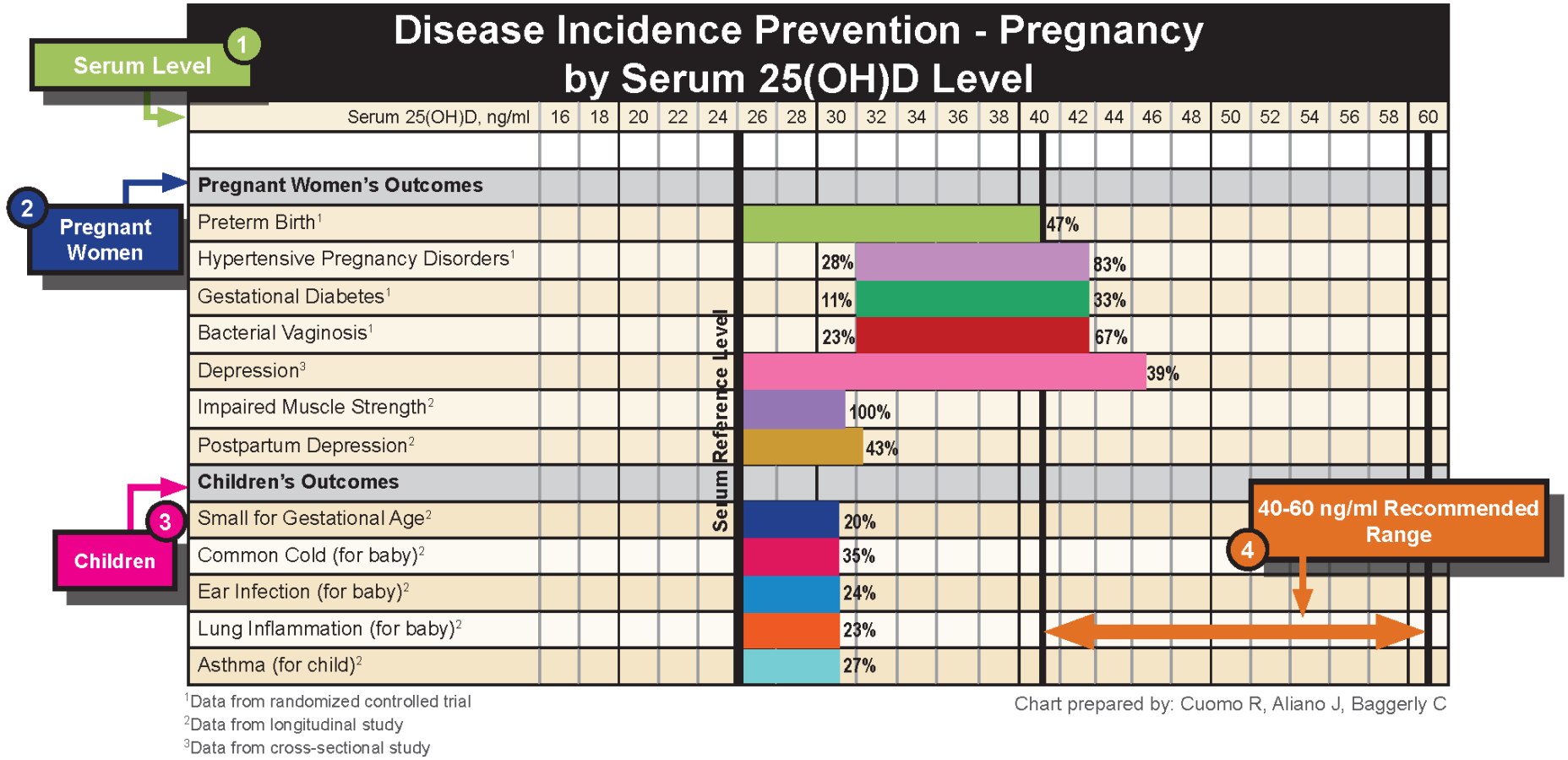
- Functions more as a hormone than as a vitamin
- Part of complex biochemical apparatus whereby multiple body systems access information stored in their DNA, enabling them to respond to signals & stimuli
- Maternal response to immune or inflammatory stimuli may be important in PTB prevention



IOM Current Recommendations for 25(OH)D

- IOM says 20 ng/ml is 'enough' for 'bone health'
- Currently being reassessed: mathematical error made in this calculation; should have been 30 ng/ml for bone health
- Optimal conversion of the 25(OH)D to the biologically active hormonal form, 1,25(OH)D occurs at approximately 40 ng/ml
- Multiple studies suggest that at least 40 ng/ml is associated with the lowest PTB rates and reductions in rates of other diseases.

Disease Prevention with Vitamin D



[1]Data from randomized controlled trial
[2]Data from longitudinal study
[3]Data from cross-sectional study

Chart prepared by: Cuomo R, Aliano J, Baggerly C

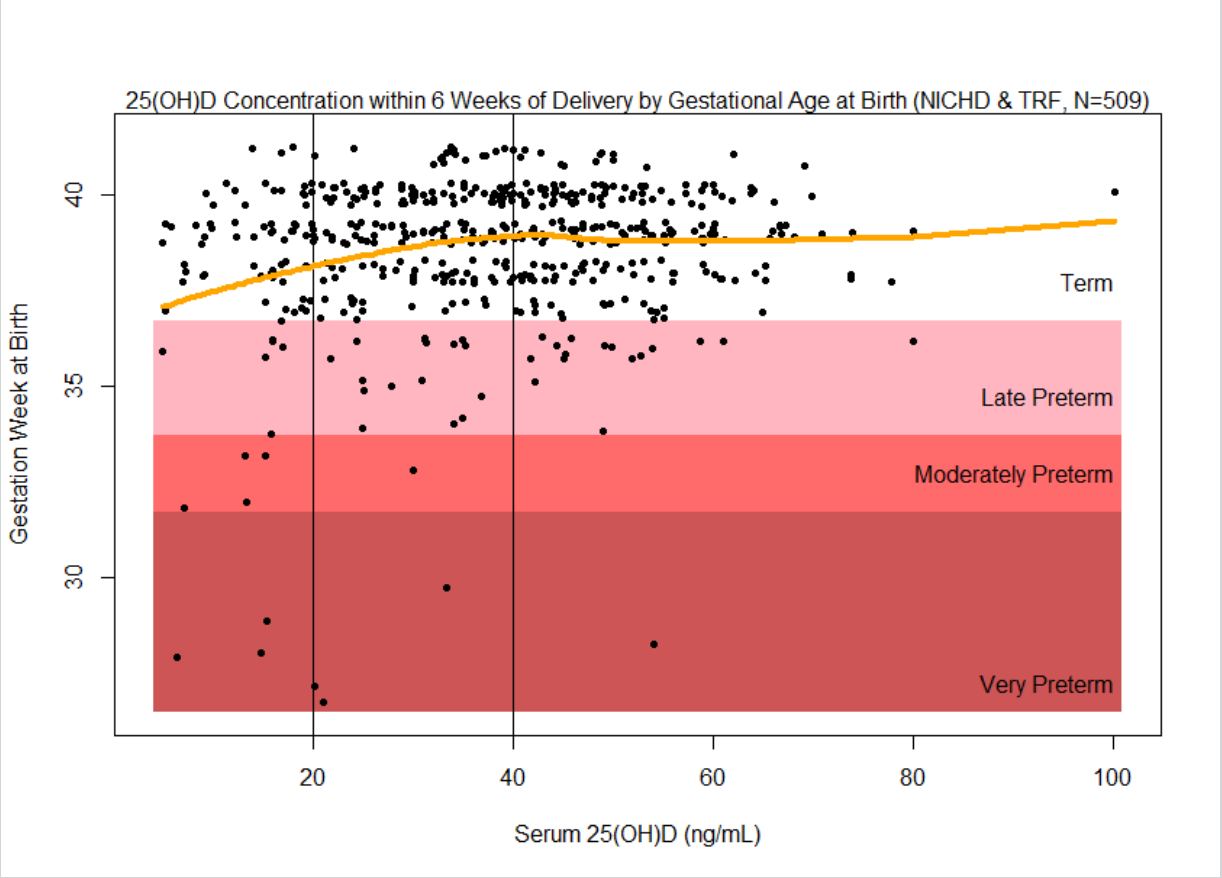
VITAMIN D AND PRETERM BIRTH

Results from two RCTs of vitamin D supplementation during pregnancy

- **Preterm birth (<37 weeks) risk is 59% lower for ≥40 ng/ml vs ≤20 ng/ml (P=0.02).**
- **Fitted LOESS curve shows gestation week at birth rising with increasing 25(OH)D (plateaus ~40 ng/ml) (figure).**

Combined NICHD and TRF cohorts (N=509)

Wagner et al. J Steroid Biochem Mol Biol. 2016



Term is ≥37 weeks, late preterm is 34 to <37 weeks, moderately preterm is 32 to <34 weeks, very preterm is <32 weeks

VITAMIN D AND PRETERM BIRTH

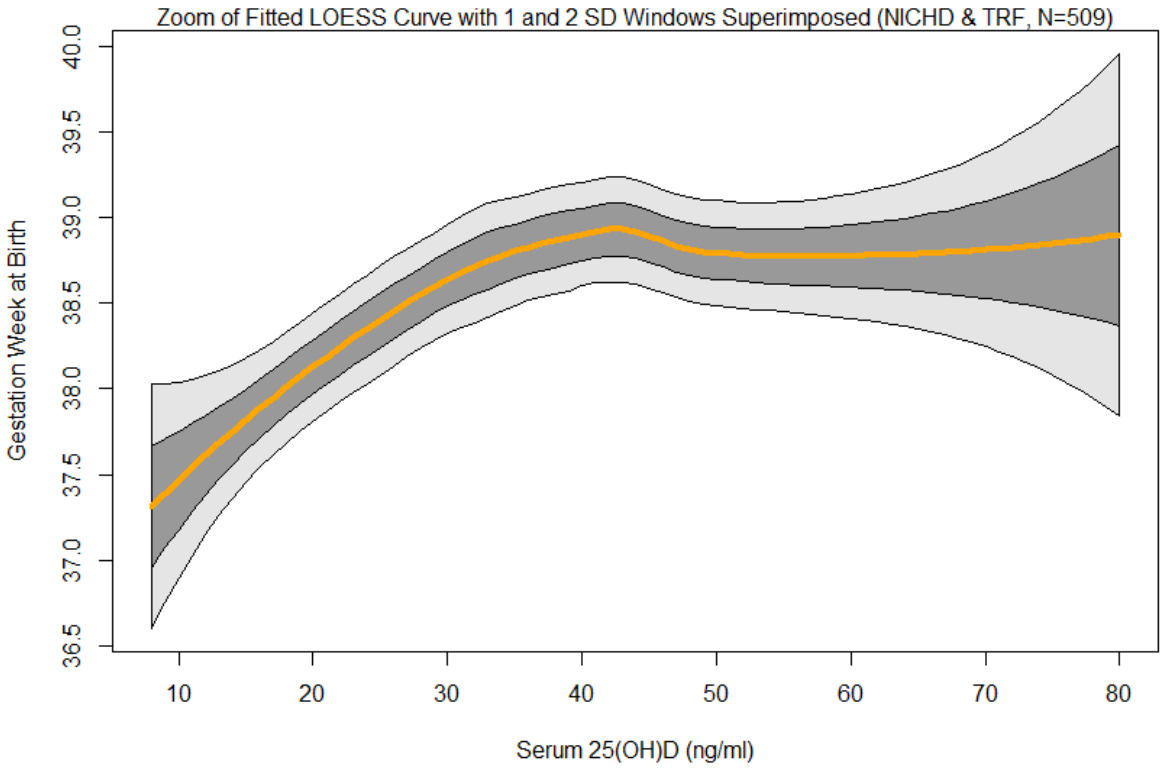
Results from two RCTs of vitamin D supplementation during pregnancy

- **Zoom of fitted LOESS curve with confidence bounds superimposed**

These findings suggest that increasing 25(OH)D concentrations to a minimum of 40 ng/ml during pregnancy could substantially reduce the risk of preterm birth.

Combined NICHD and TRF cohorts (N=509)

Wagner et al. J Steroid Biochem Mol Biol. 2016



Black line represents fitted LOESS curve; dark gray area represents 1 standard deviation; and light gray area represents 2 standard deviations

MUSC Preterm Birth Prevention Field Trial

Vitamin D Screening and Supplementation Program

- Objective: to determine if the inverse relationship between 25(OH)D levels and PTB rate seen in the RCTs could be replicated in a clinical field trial involving a large and diverse general obstetrical population

- A vitamin D screening and supplementation program was implemented in September 2015 at the Medical University of South Carolina.
  - Routine vitamin D screening for pregnant women at first prenatal visit.
  - Follow-up testing for those <40 ng/ml at 24-28 weeks and prior to delivery.
  - Obstetrical health care providers received CME regarding potential health benefits of sufficient vitamin D status.
  - Standard recommendations provided for aggressive vitamin D supplementation depending on baseline vitamin D status.
  - Free samples of vitamin D provided to deficient women

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Vitamin D Screening and Supplementation Program

Characteristic	Field Trial Cohort (n=1,064)
Race/ethnicity (n,%) White Black Hispanic Asian/PI Multiple/Other	 488 (46%) 395 (37%) 117 (11%) 19 (2%) 39 (4%)
Maternal age, yrs (median/range)	29 (18-45)
Gravidity (median/range)	2 (1-11)
Parity (median/range)	1 (0-9)
Pre-pregnancy BMI (median/range)	25 (12-66)
Married (n,%)	530 (50%)
Education, yrs (median/range)	13 (4-20)
Prior preterm birth (n,%)	140 (13%)
Preterm birth <37 wks (n,%)	139 (13%)

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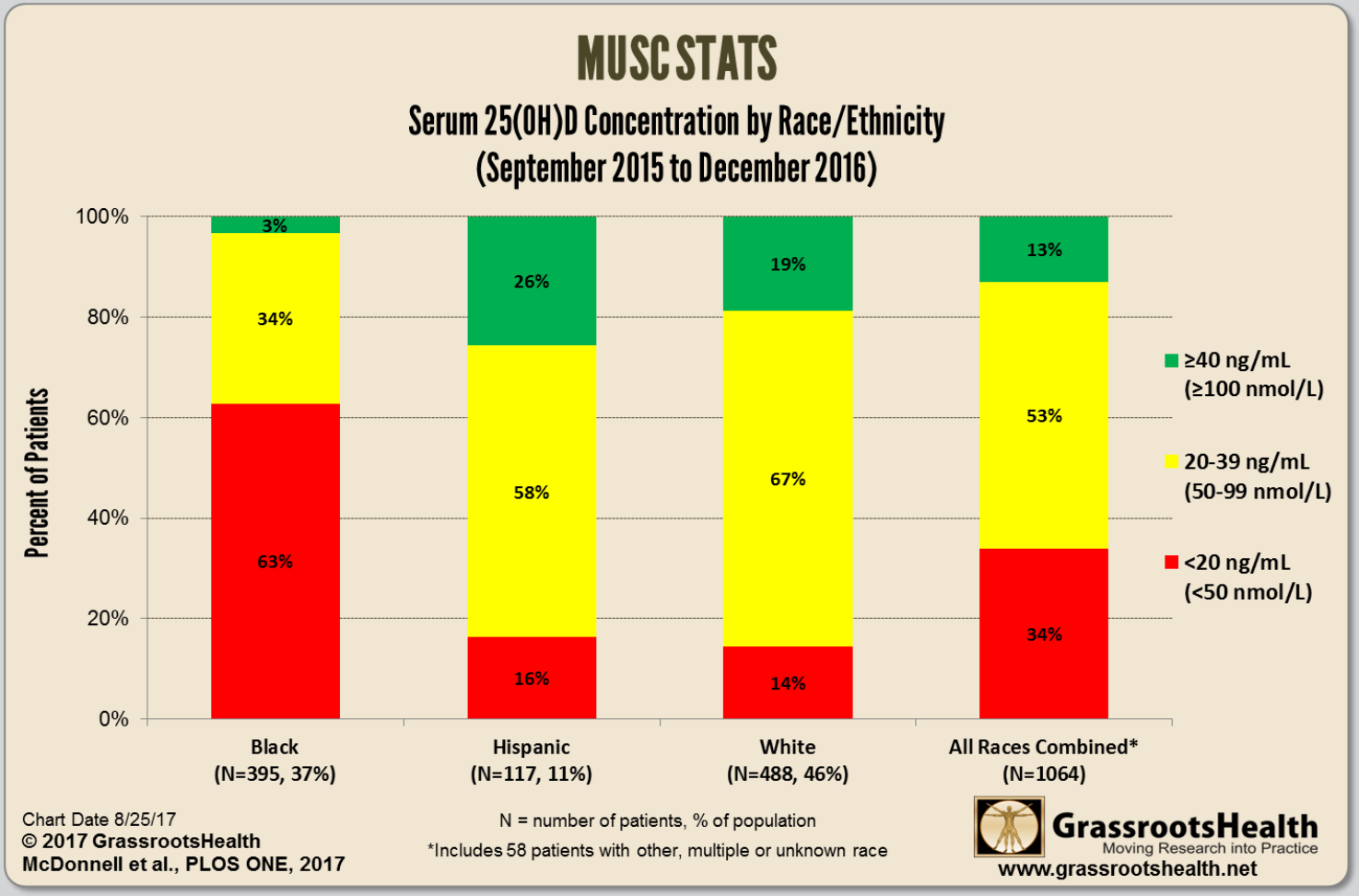
Vitamin D Screening and Supplementation Program

- Overall, ~90% had levels <40 ng/ml
- 97% of black women had levels <40 ng/ml
- One-third of all women (two-thirds of blacks) < 20ng/ml



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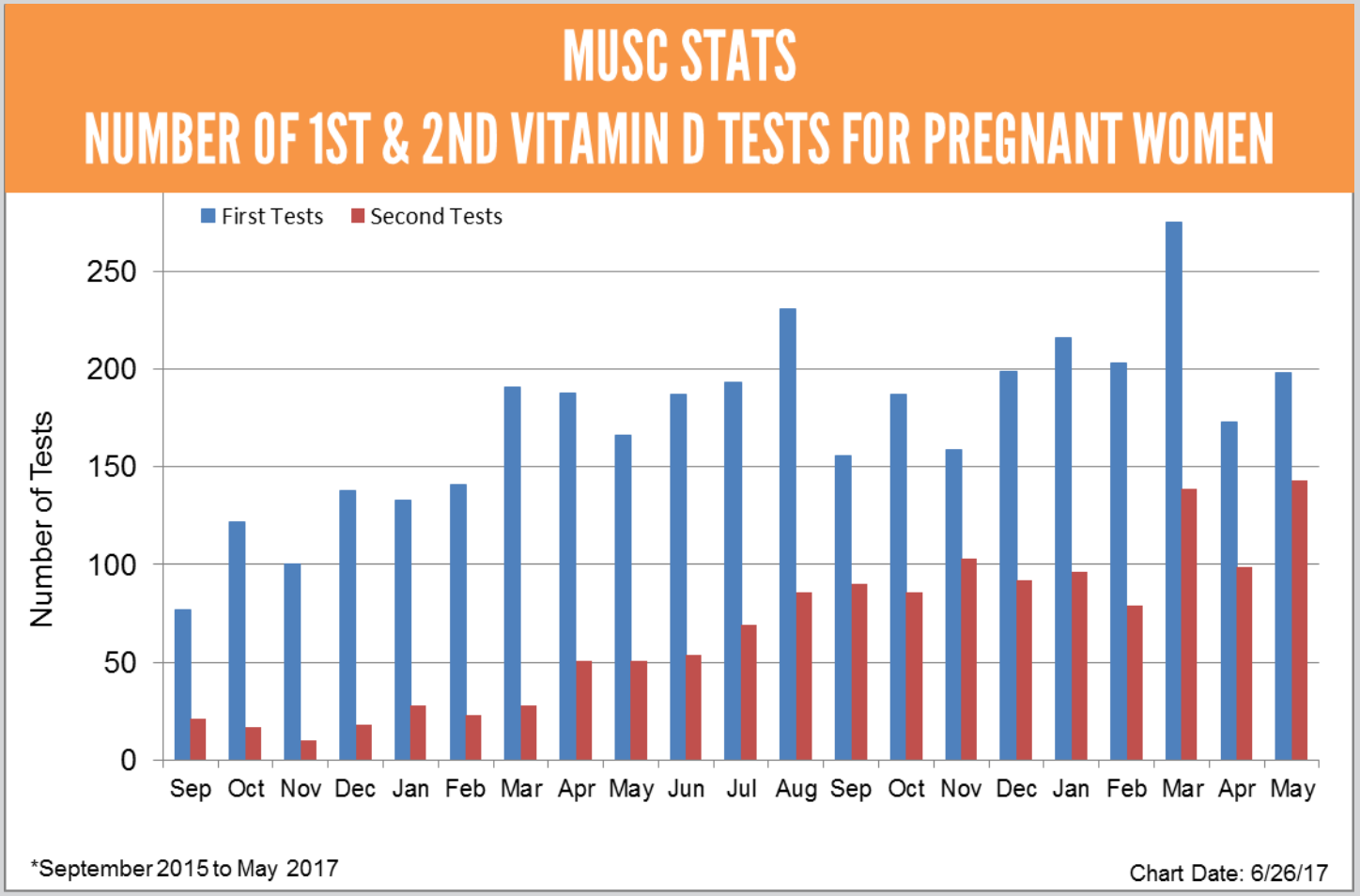
- Number of first tests increased from ~100 to ~200 per month.
- Number of second tests increased from ~20 to ~125 per month.



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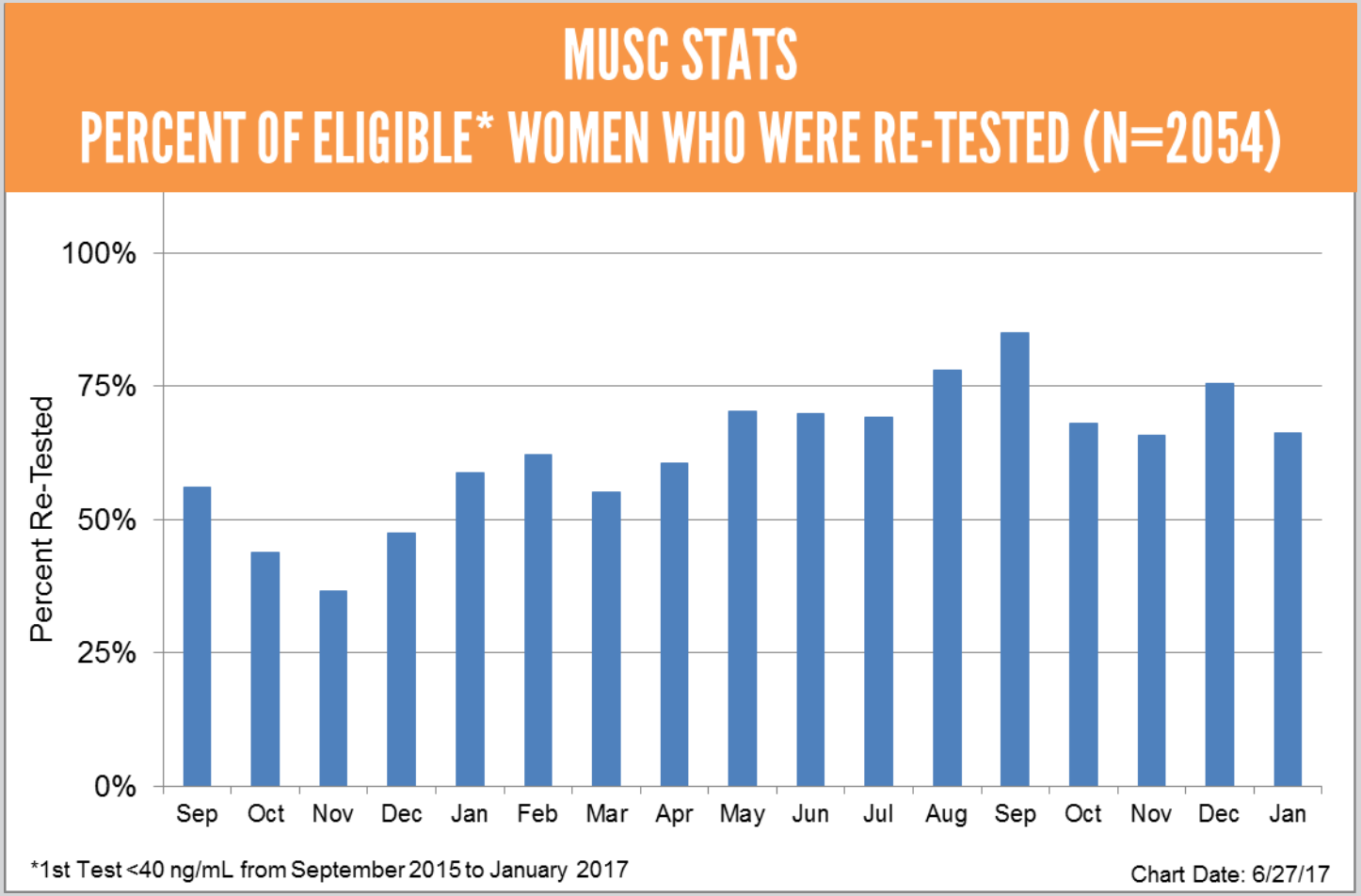
- Re-testing has increased over time, but has but has plateaued ~70%.
- Automatic re-testing at 28 weeks is being implemented.



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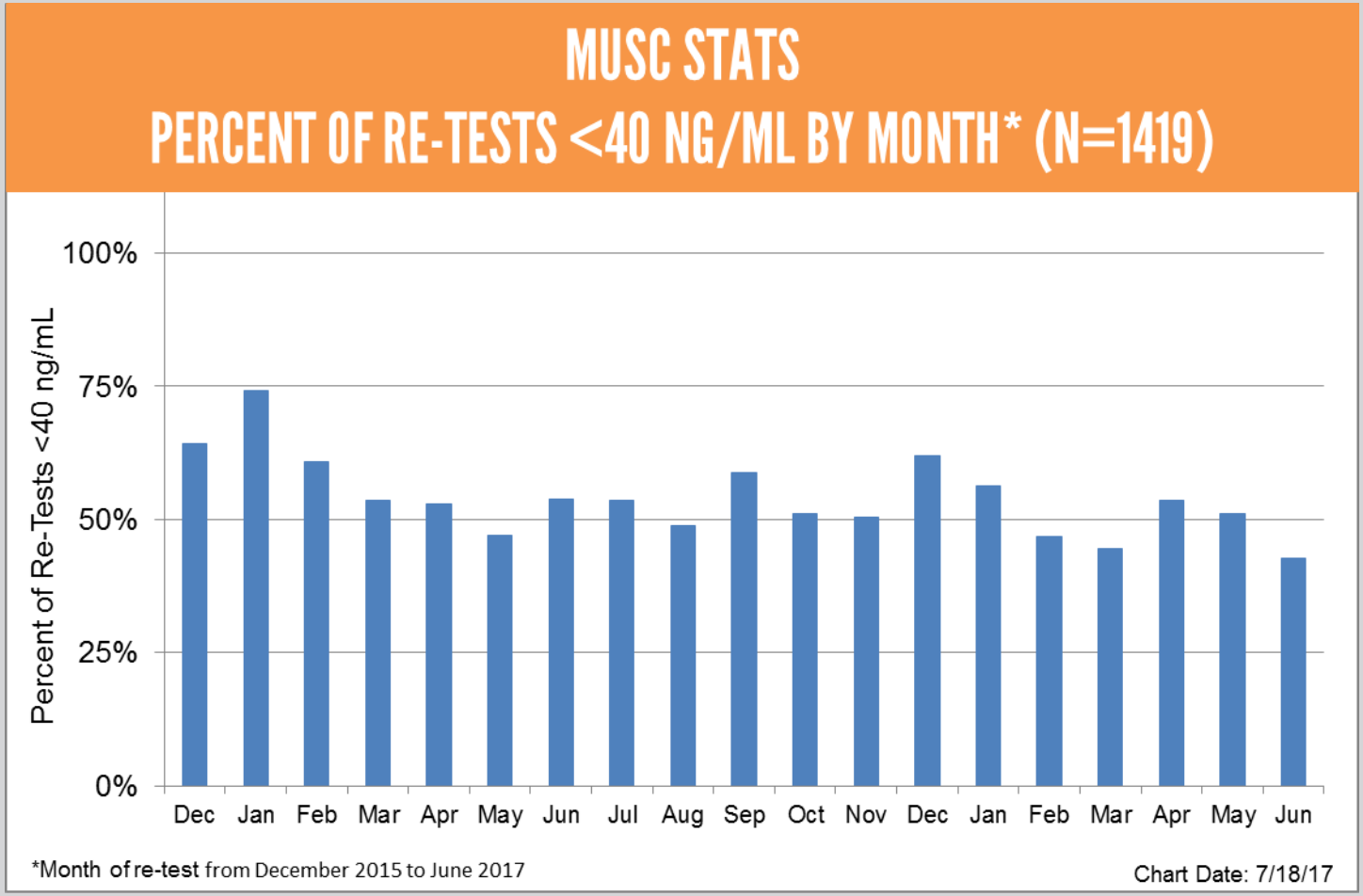
- The proportion of women not reaching at least 40 ng/ml has decreased over time but has plateaued ~45%.



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Vitamin D Screening and Supplementation Program

- Between September 2015 and December 2016, delivery information is available for 1,064 women with at least one 25(OH)D test result during pregnancy.

- There were 139 (13.1%) preterm births (<37 weeks)
  - 20 (1.9%) were “very preterm” (<32 weeks)
  - 21 (2.0%) were “moderately preterm” (32 to <34 weeks)
  - 98 (9.2%) were “late preterm” (34 to <37 weeks)

McDonnell et al., PLOS ONE, 2017

MUSC Preterm Birth Prevention Field Trial

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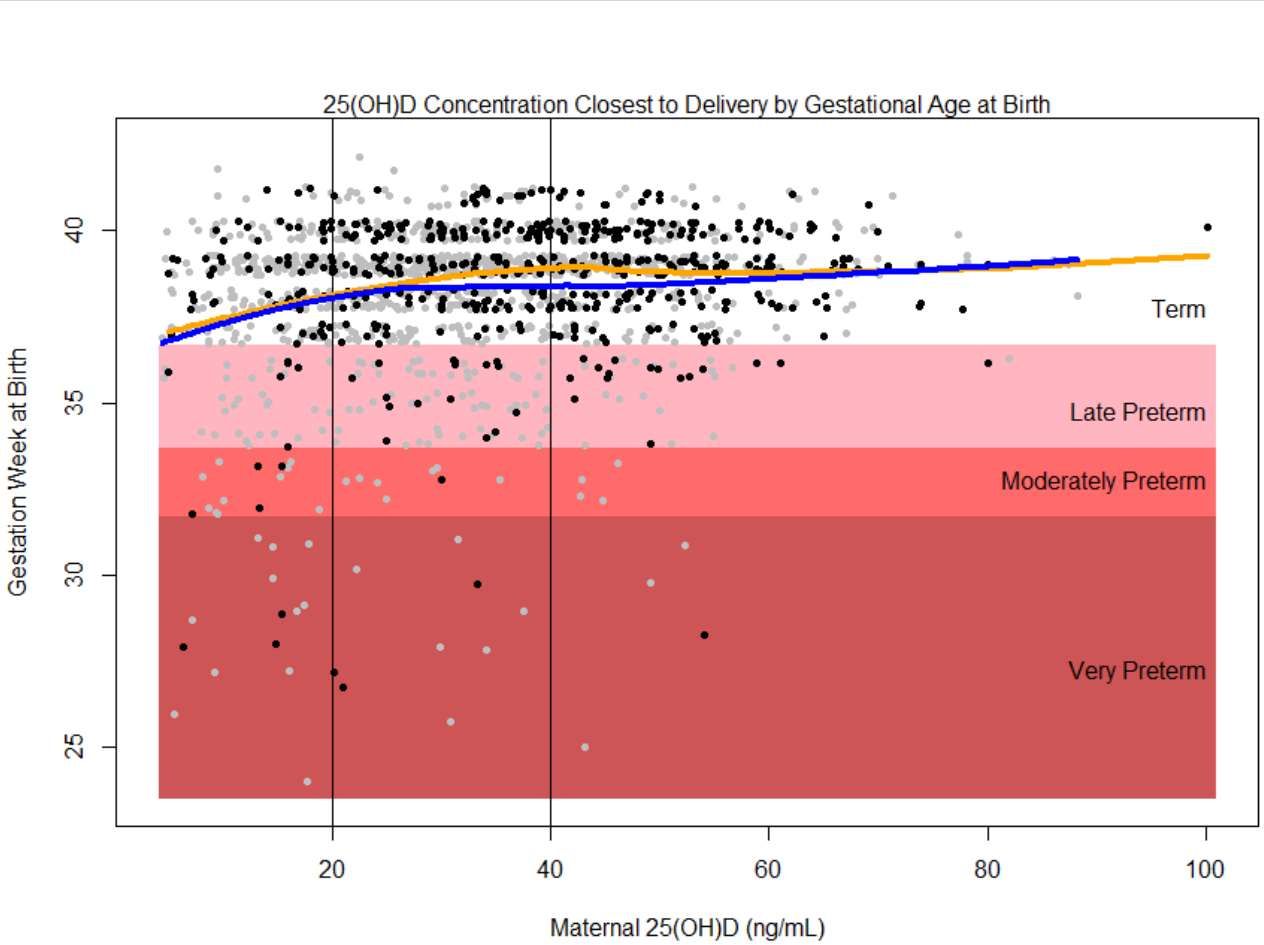
Vitamin D	PTB < 37 wks	Term Birth >=37 wks	P-value (test for trend)	OR (95%CI)
<20 ng/ml N (%)	49 (19.8%)	199 (80.2%)		1.0 Ref
20 - <30 ng/ml N (%)	33 (12.4%)	234 (87.6%)		**0.57 (0.35,0.93)**
30 - <40 ng/ml N (%)	32 (12.5%)	223 (87.5%)		**0.58 (0.36,0.95)**
>= 40 ng/ml N (%)	25 (8.5%)	269 (91.5%)	**0.0003**	**0.38 (0.23,0.63)**

62% lower risk for preterm birth (<37 weeks) for those with 25(OH)D ≥40 ng/ml vs. <20 ng/ml (P<0.0001)

McDonnell et al., PLOS ONE, 2017

MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

- **Fitted LOESS curve of field trial data (blue line) is closely tracking the LOESS curve of the Wagner RCT data (orange line) (figure).**



Black circles & orange line = Wagner RCTs (N=509), gray circles & blue line = MUSC field trial (N=1064).

McDonnell et al., PLOS ONE, 2017

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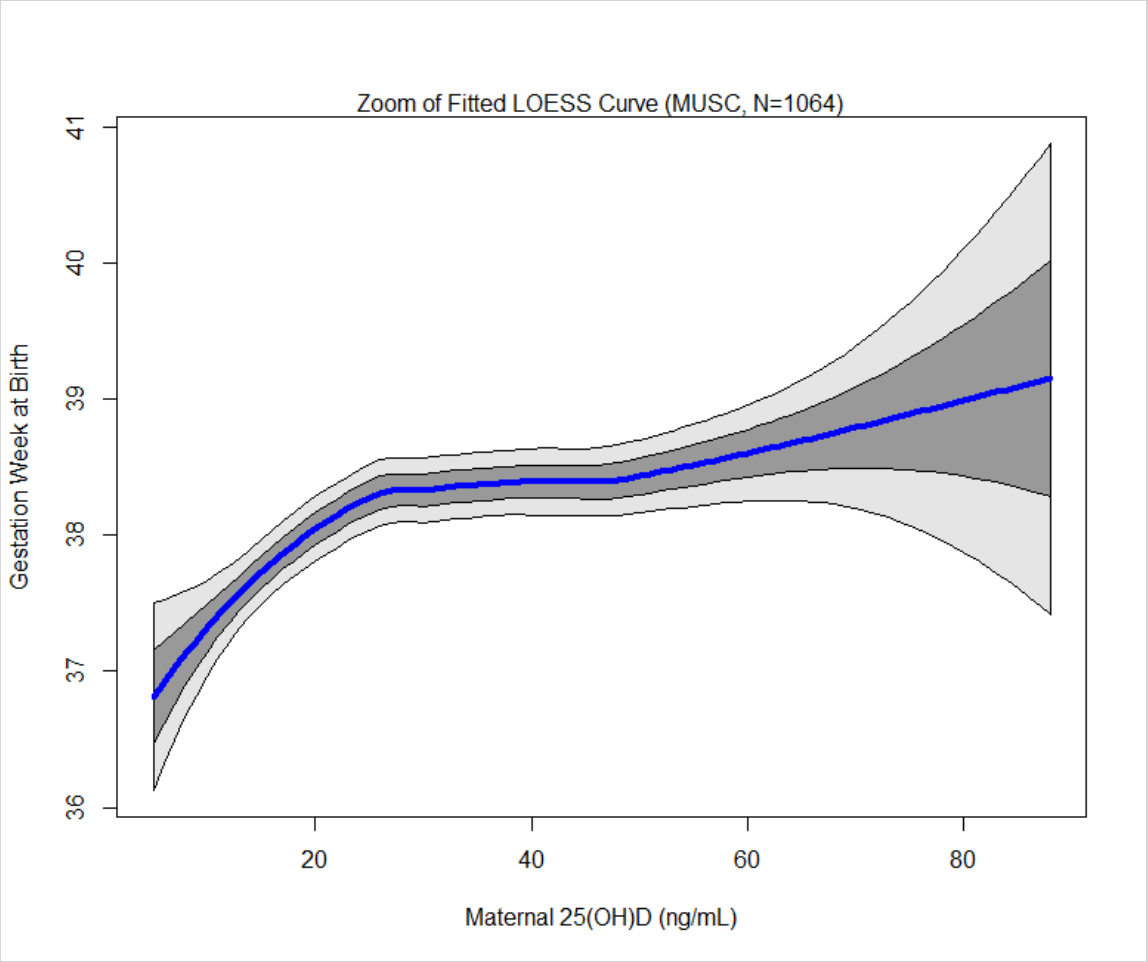
- **Zoomed LOESS Curve: Gestational age rising with increasing 25(OH)D.**

These field trial findings suggest that increasing 25(OH)D concentrations to 40 ng/ml during pregnancy could reduce the risk of preterm birth by > 50%.



Blue line represents fitted LOESS curve; dark gray area represents 1 standard deviation; and light gray area represents 2 standard deviations.

McDonnell et al., PLOS ONE, 2017

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Vitamin D	White Women (N=488)	Non-White Women (N=570)
<20 ng/ml N preterm/N total (%)	7/30 (23.3%)	40/216 (18.5%)
20 to <30 ng/ml N preterm/N total (%)	8/120 (6.7%)	25/145 (17.2%)
30 to < 40 ng/ml N preterm/N total (%)	16/149 (10.7%)	16/106 (15.1%)
>= 40 ng/ml N preterm/N total (%)	18/189 (9.5%)	7/103 (6.8%)

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- **65% lower risk of PTB** among white women with 25(OH)D ≥40 ng/ml compared to <20 ng/ml **(OR=0.35,95% CI 0.13-0.92,p=0.03)**
- **68% lower risk of PTB** among non-white women with 25(OH)D ≥40 ng/ml compared to <20 ng/ml **(OR=0.32,95% CI 0.14-0.74,p=0.008)**
- **80% lower risk of PTB** among women with a prior PTB with 25(OH)D ≥40 ng/ml compared to <20 ng/ml **(OR=0.20,95% CI 0.05-0.74,p=0.02)**

McDonnell et al., PLOS ONE, 2017

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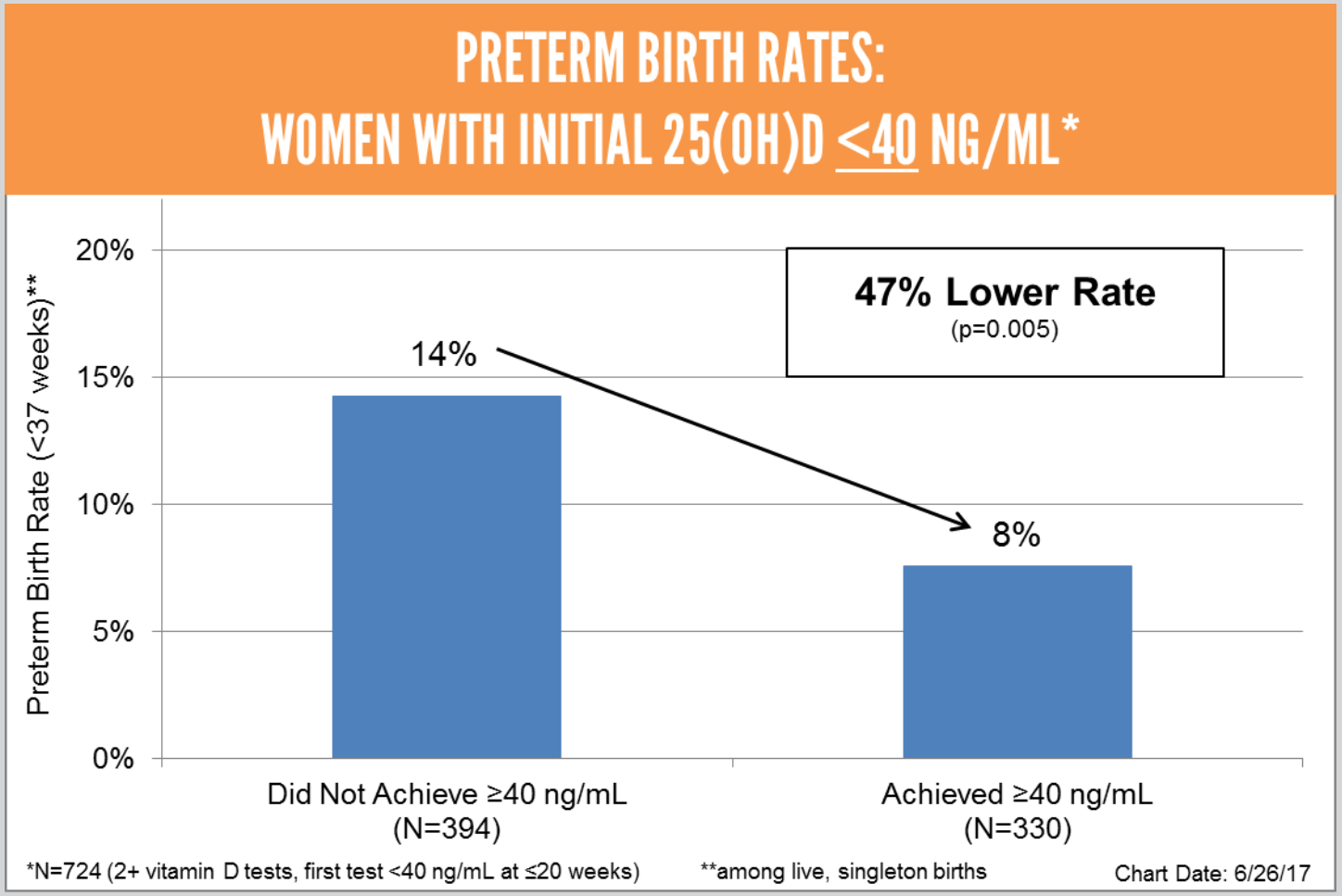
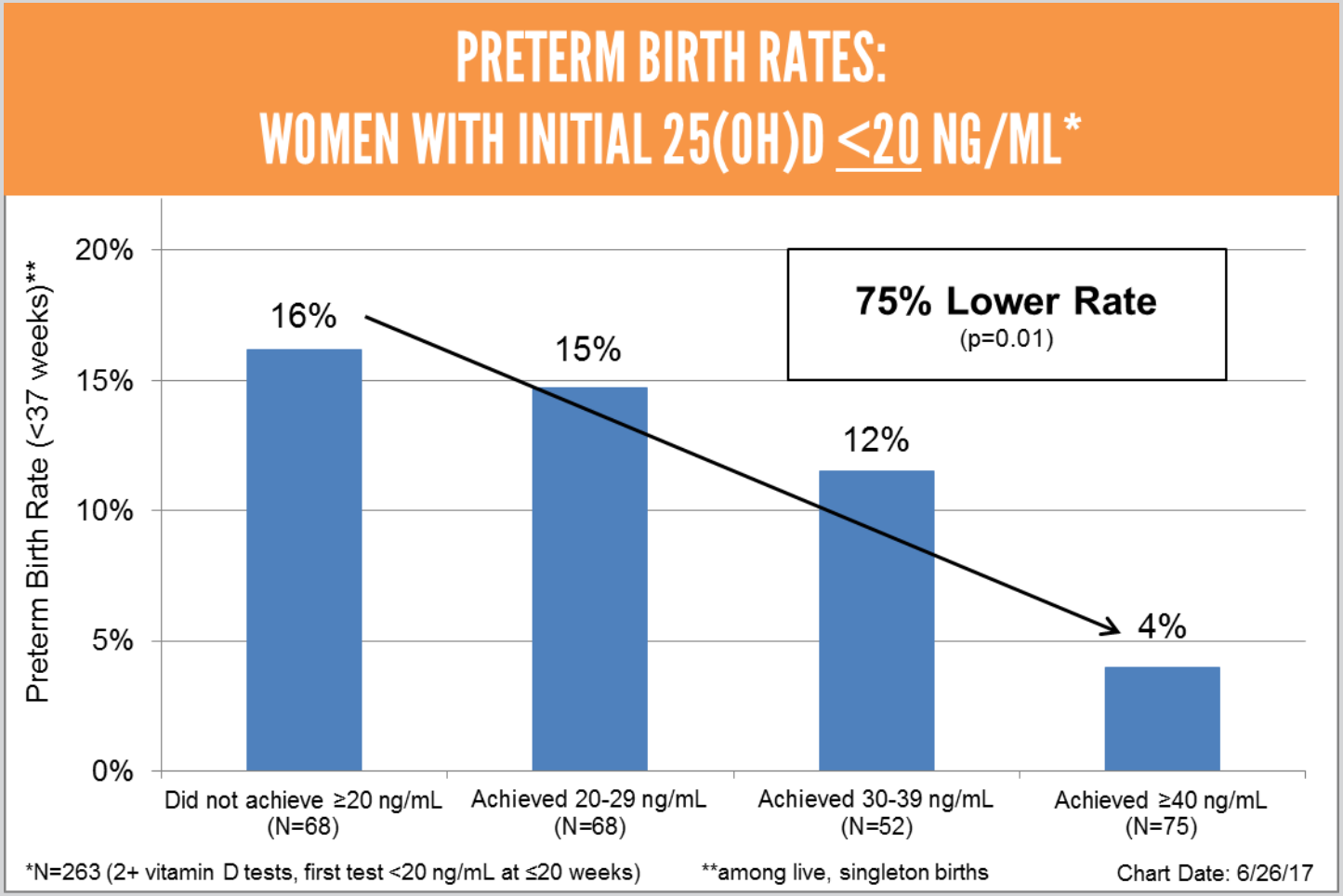
Vitamin D Screening and Supplementation Program



Data:
Sep. 2015 to
May 2017

MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program



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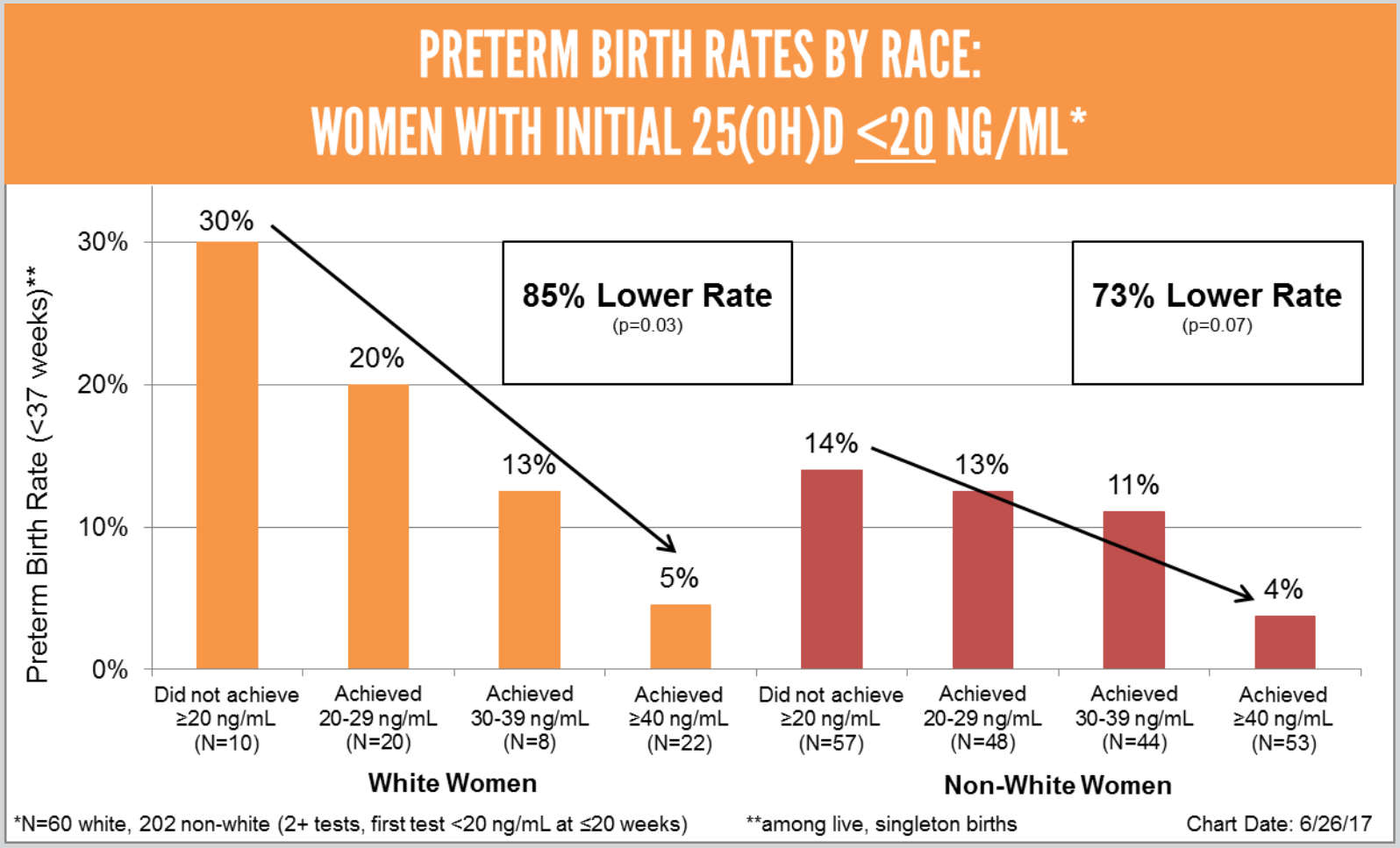

Data: Sep. 2015 to May 2017

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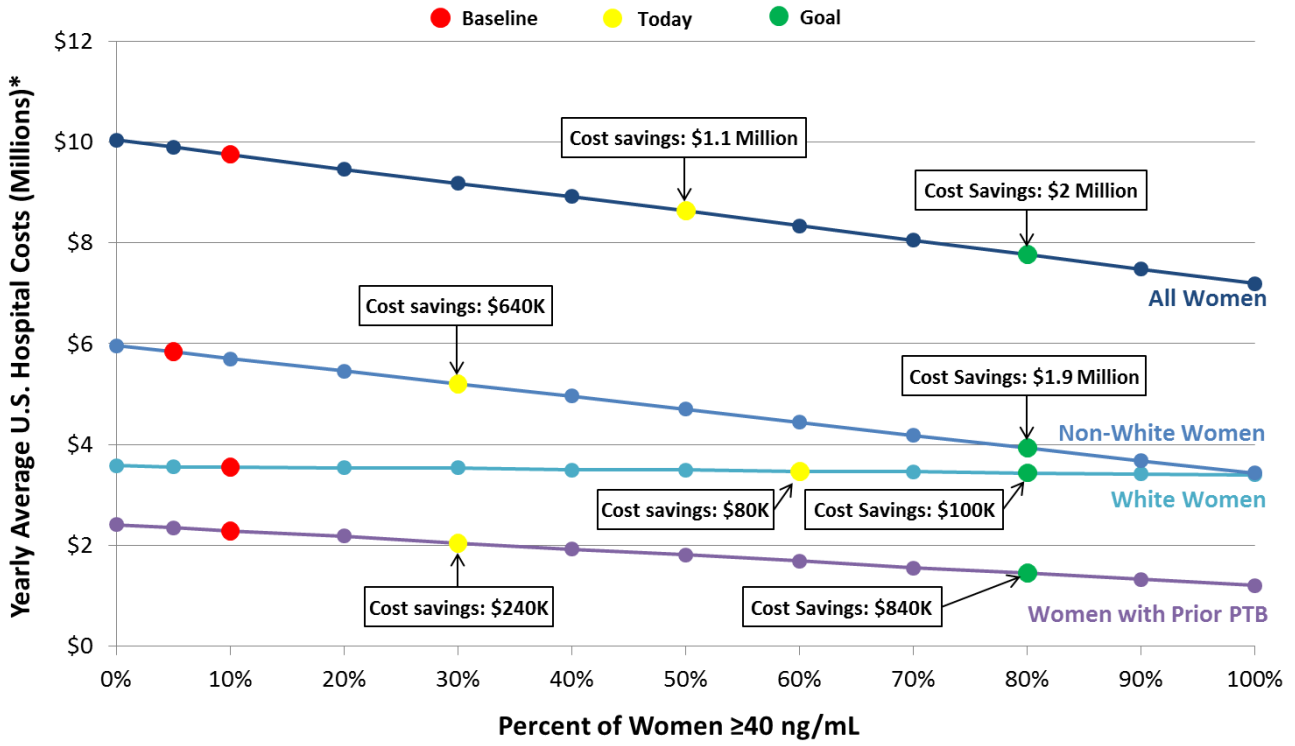
- Only used newborn hospital costs Estimate another $30k over first year.
- Racial disparity goes away with vitamin D levels >40 ng/ml.



*Average U.S. hospital costs are $21,500 for preterm (<37 weeks) vs. $1,500 for term (Healthcare Cost and Utilization Project: Hospital Stays for Newborns, 2011). Based on 2250 women with live, singleton birth and prenatal care at MUSC per year (1200 for non-whites, 1000 for whites, 300 for prior PTB). PTB rates are 14.8% for <40 and 8.5% for ≥40 ng/mL (McDonnell et al., PLOS ONE, 2017) (17.3% vs. 6.8% for non-whites, 10.4% vs. 9.5% for whites, 32.8% vs. 12.5% for prior PTB). Baseline and re-testing ('today') proportions from McDonnell et al., PLOS ONE, 2017.

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- **Major Learnings to Date:**
  - **There is a statistically significant reduction in preterm birth as a result of getting vitamin D levels to at least 40 ng/ml; matching the RCT results.**
  - **Obtaining accurate and timely data from the IT system is key to performance changes**
  - **Physicians and staff have been active participants but require extensive CME and in-service education**
  - **Obtaining insurance organization support for testing has also been key**

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- **Next Steps:**
  - Continuing collecting Vitamin 25(OH)D baseline and pregnancy outcome data
  - Targeted new goals for MUSC clinics and physicians: increase re-testing and achievement of > 40 ng/ml to 80%
  - Provide free Vitamin D supplements with 5000 IU tablets
  - Translate results to other new OB care providers and organizations
  - Efforts supported by GrassrootsHealth; non-profit public health organization
  - New outcome analyses associated with vitamin D deficiency
    - Use of 17p/progesterone to prevent PTB
    - Prenatal: pre-gestational diabetes, GDM, obesity, pre-eclampsia
    - Childhood: obesity, MS, childhood atopy, asthma and autism; integration with state's health outcomes database