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Maternal and Child Micronutrient Deficiencies and the First 1,000 Days of Life: Asian Perspectives

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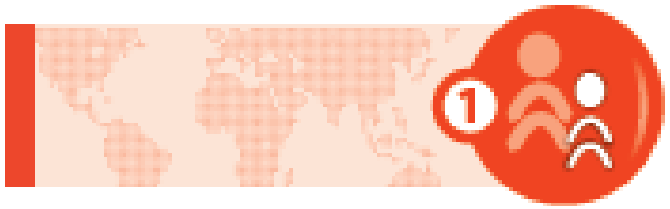
Presented at the 14th APPSGHAN, Bangkok, Thailand (October 25, 2018)

Outline

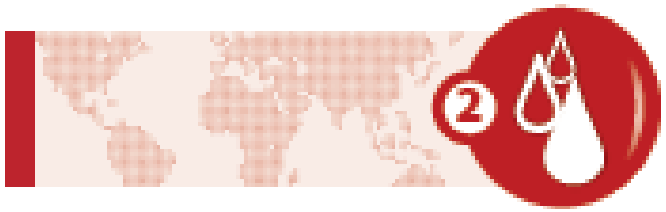
1) Introduction: Why micronutrients matter in the first 1,000 days?
2) Key micronutrients of public health importance in Asia and current issues

1) **Multiple micronutrient supplementation** during pregnancy
2) Benefit vs risk of iron supplementation
3) **Iodine supplementation** and child outcomes

Global Nutrition Target for 2025

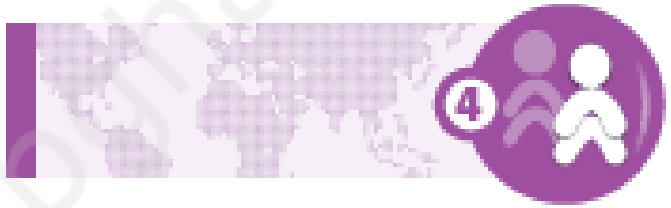


40% reduction in the number of children under 5 who are stunted

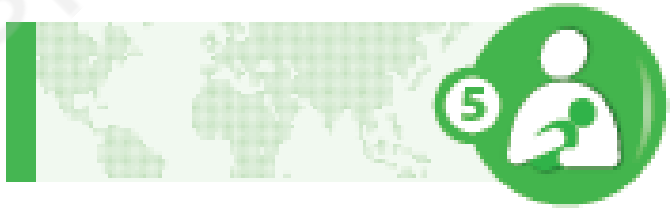


50% reduction of anemia in women of reproductive age

30% reduction in low birth weight

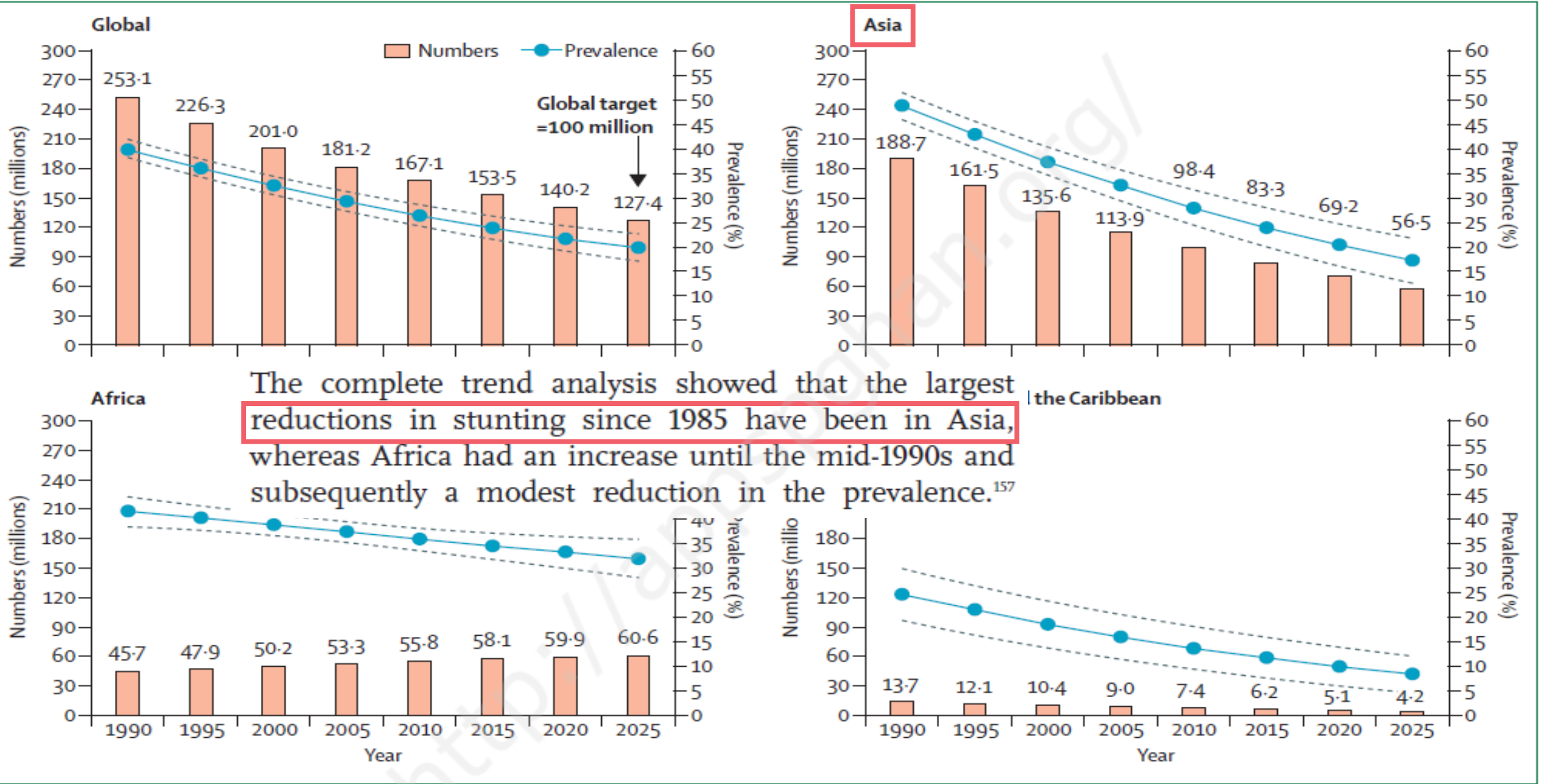


No increase in childhood overweight



Increase the rate of exclusive breastfeeding in the first 6 months up to at least 50%

Reduce and maintain childhood wasting to less than 5%

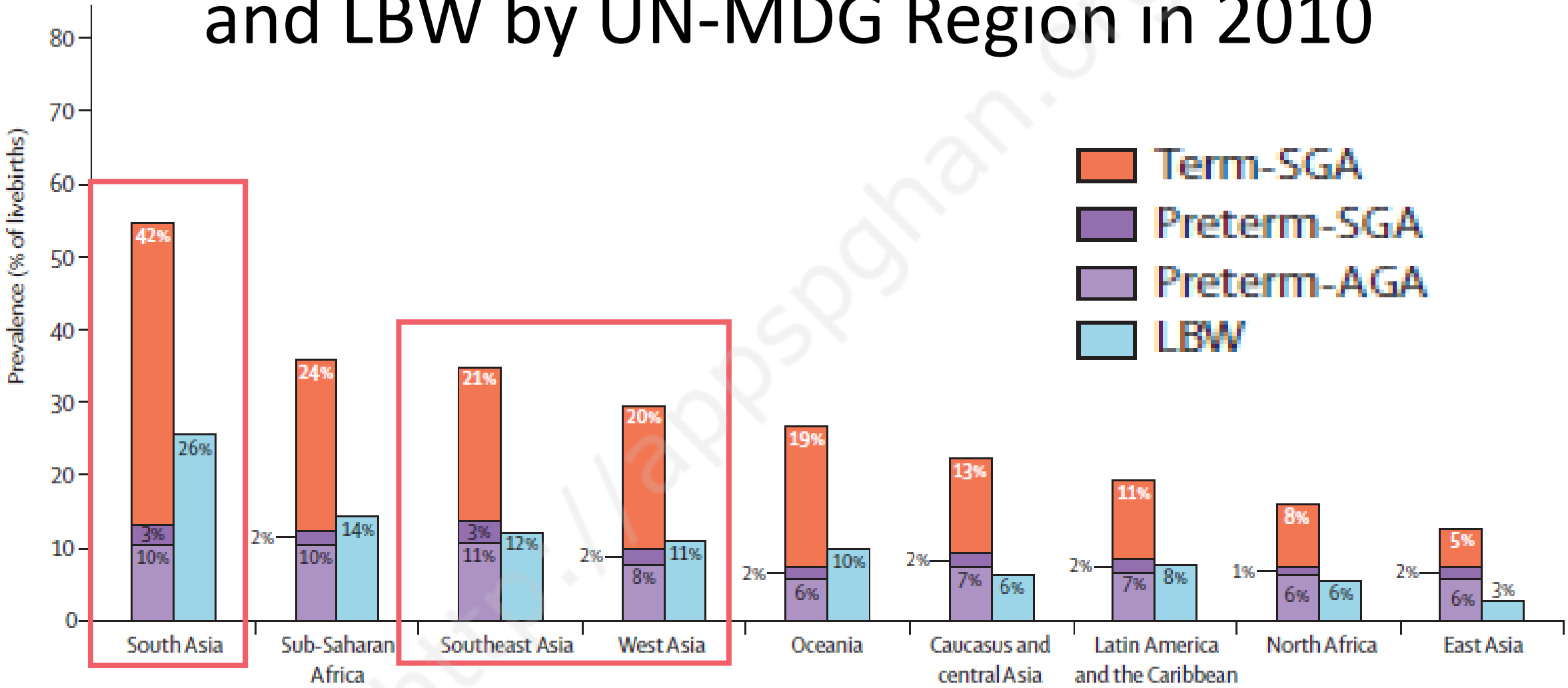


The complete trend analysis showed that the largest reductions in stunting since 1985 have been in Asia, whereas Africa had an increase until the mid-1990s and subsequently a modest reduction in the prevalence.[157]

Figure 4: **Trends in prevalence and numbers of children with stunted growth (HAZ <–2), by selected UN regions and globally, 1990–2010, and projected to 2025 on the basis of UN prevalence estimates**

HAZ=height-for-age Z score. Data from UNICEF, WHO, World Bank.[154]

Prevalence of SGA, Preterm Births, and LBW by UN-MDG Region in 2010



AGA=appropriate for gestational age. SGA=small for gestational age. LBW=low birthweight.

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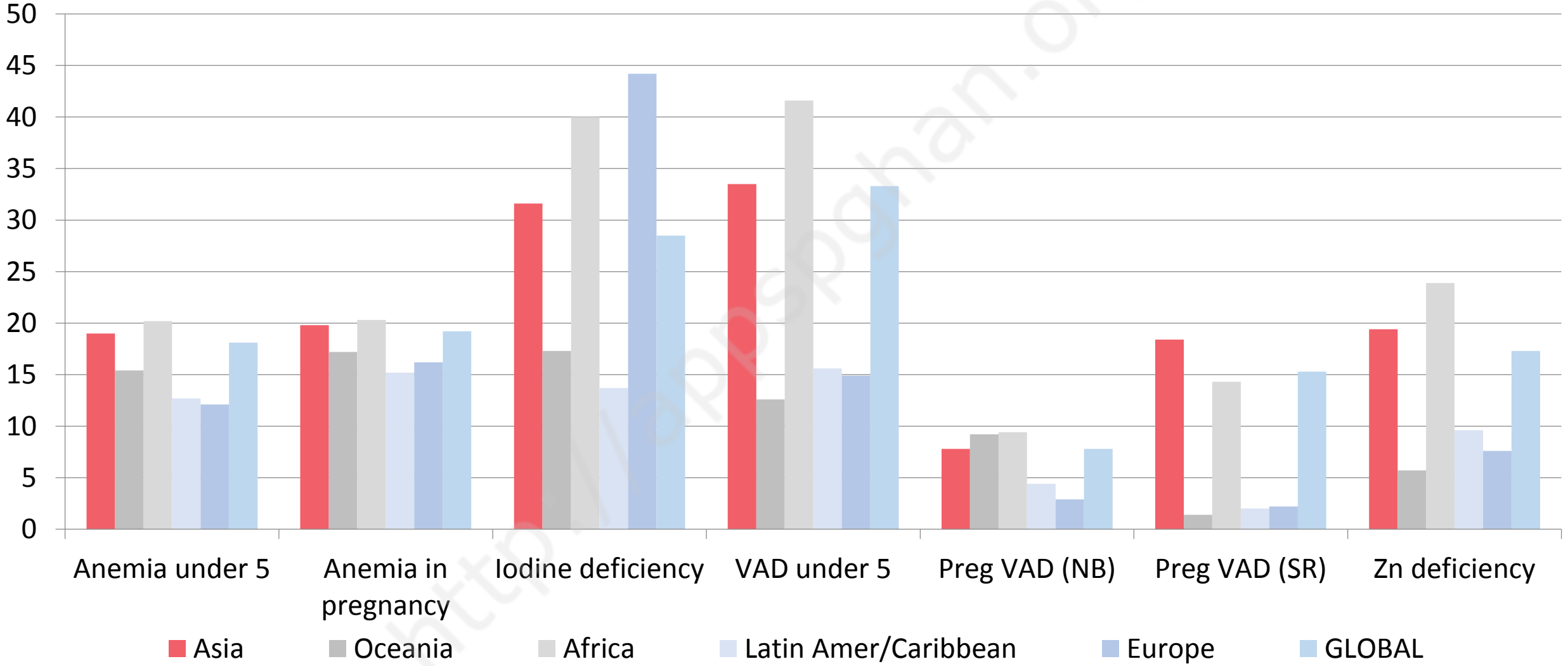
Global & Regional Situation of Key Micronutrient Deficiencies in LMIC, PREVALENCE (%)



Black, et al, MCN Lancet series, 2013

What is the 1000 days?

Conception	Child birth	2 y of age

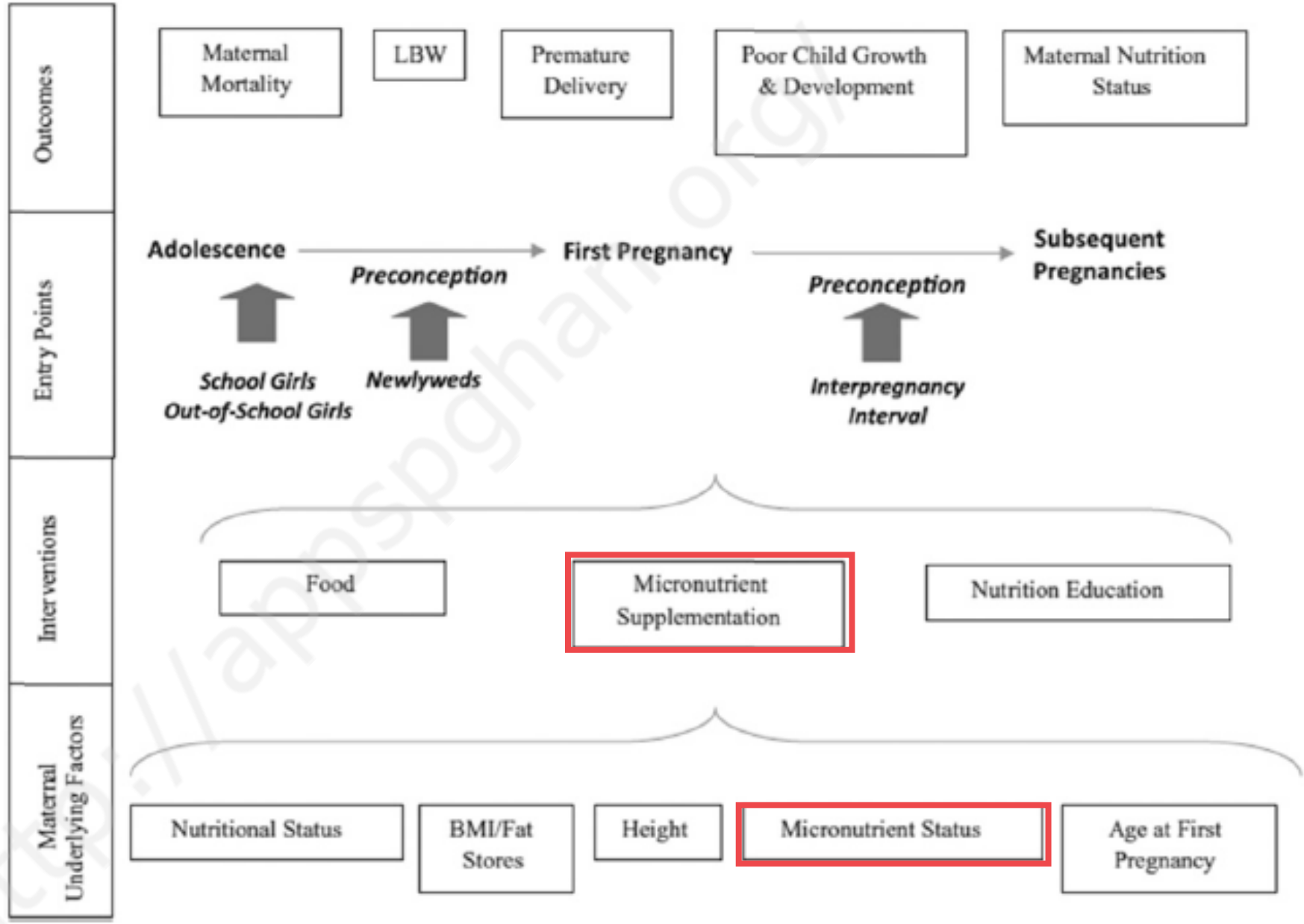
Micronutrient Deficiencies During Pregnancy

- Iron-deficiency anemia (IDA)
  - Increased risk of low birthweight and maternal mortality
- Vitamin A deficiency (VAD)
  - Associated with poor birth outcomes and infant mortality
- Severe Iodine deficiency disorders (IDD)
  - Can cause pregnancy loss, mental retardation, and cretinism
- Vitamin D insufficiency
  - Still have been reported even in tropical areas
- Zinc deficiency
  - May cause pregnancy complications
- Folate deficiency
  - Results in neural tube defect

Several micronutrients are important for fetus

- Fetus growth: Iron, iodine, zinc, folate (prepregnancy), vitamin B_6, Vitamin A
- Fetal brain: Iodine, iron, zinc, folate, choline
- Fetus status/stores at birth: iron, vitamin A, E, D, B_{12}, B_6, B_2

Maternal nutrition and interventions potentially affect child growth and development outcomes



Ramkrishnan, et al, Paediatr Perinat Epidemiol 2012

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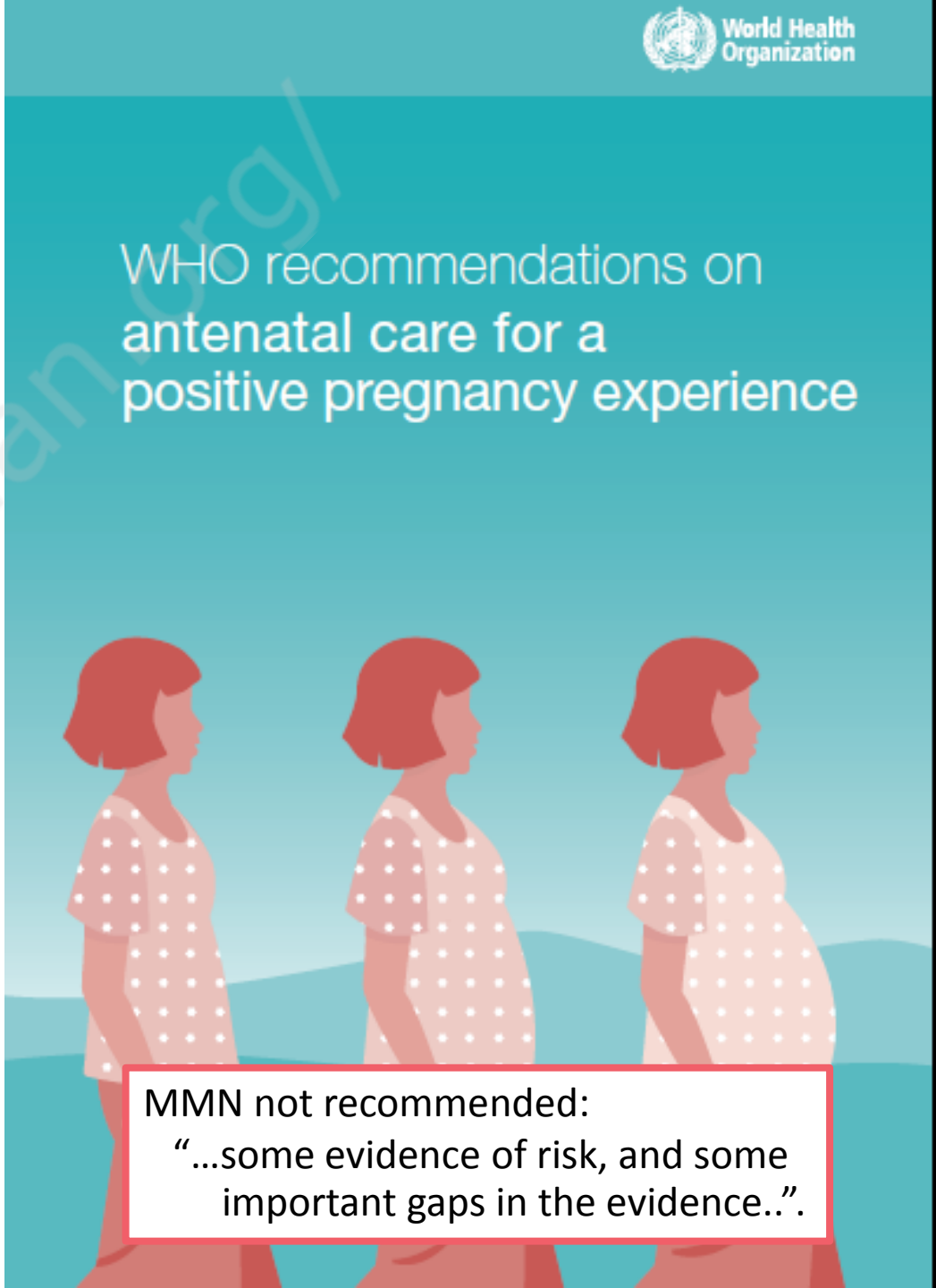
WHO Recommendation on Antenatal Care (2016)

- Comprehensive guideline for ANC through technical consultation on evidence-based interventions
- Nutrition interventions
  1. Dietary interventions
  2. Vitamins and mineral supplements:
     - Recommended (birth outcomes):
       - Iron/folate supplement
       - Calcium* – pre-eclampsia
       - Vit. A* – severe (night blindness)
       - Zinc* (research support)
     - Not recommended:
       - MMN, B6, vit. E, C, D

* context-specific



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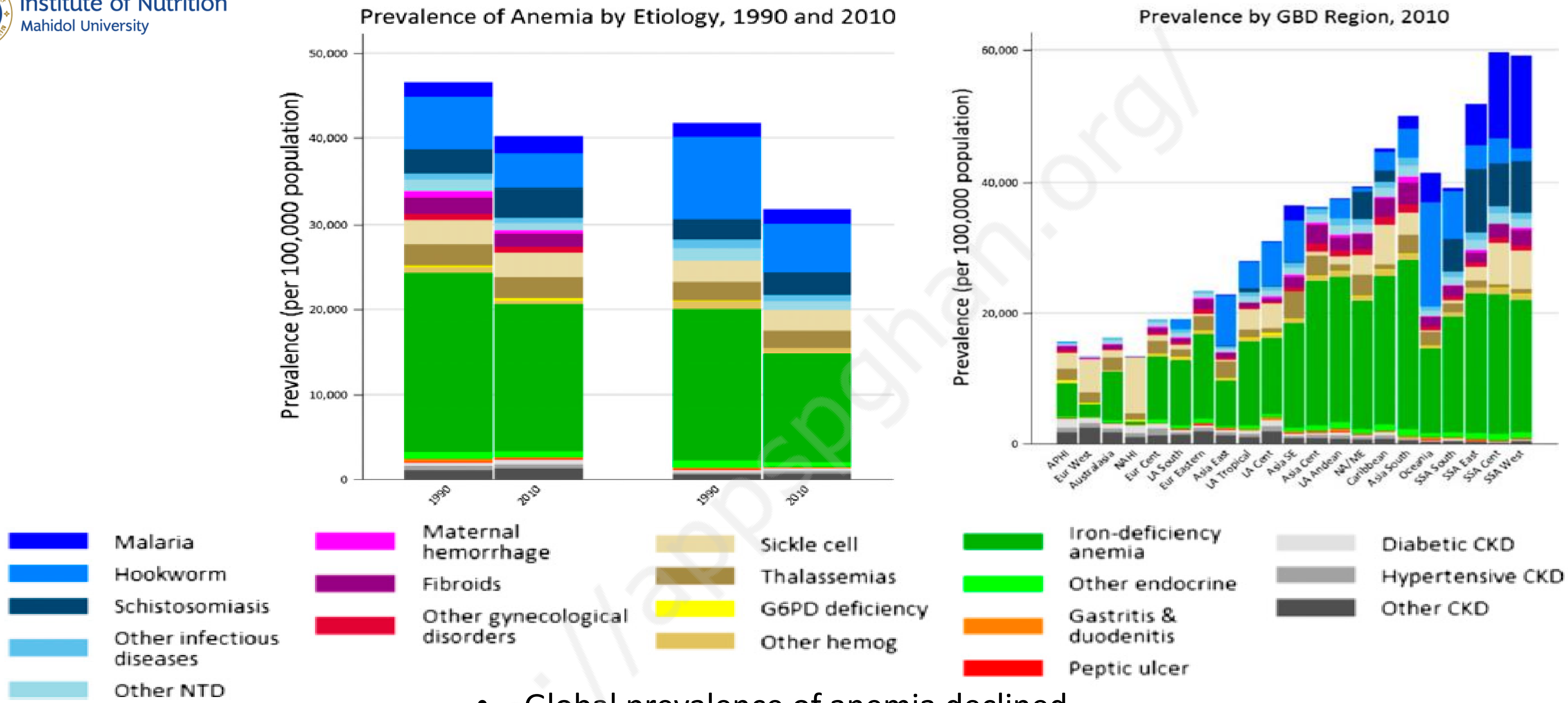
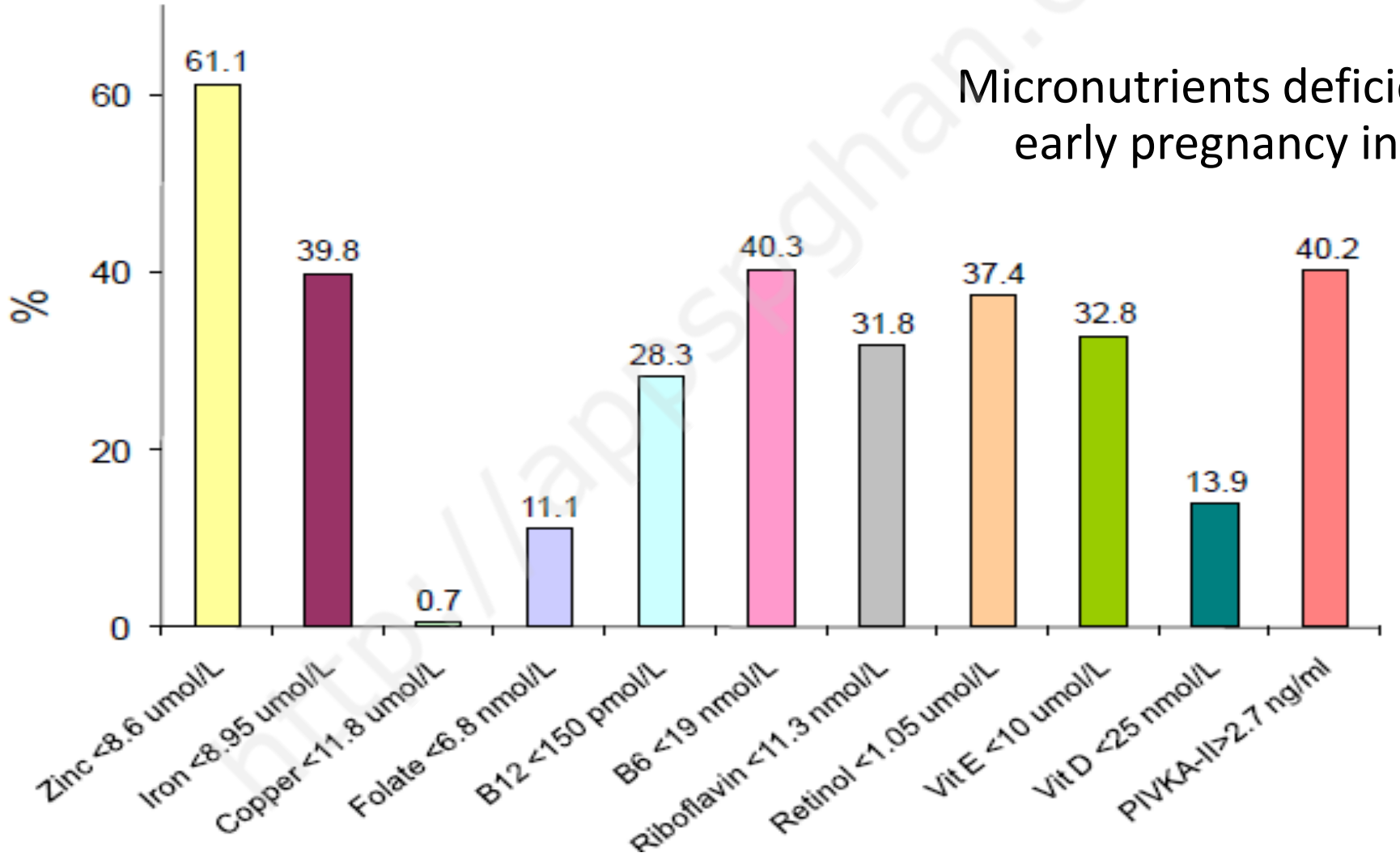


- Global prevalence of anemia declined
- Prevalence of anemia highest in Africa, but # affected higher in Asia
- Ranking of causes in Asia
  1. Iron deficiency 2. Hookworm 3. Thalassemia
  4. Malaria 5. Sickle cell disorders

Kassebaum, et al, Blood 2014

Micronutrient Deficiencies May Coexist at Population and Individual Level

Micronutrients deficiencies in early pregnancy in Nepal



Jiang, et al, JN 2005

Systematic Review and Meta-analysis of the Effect of Iron Containing Supplements

Supplementation during pregnancy:

1. Iron and folic acid (IFA) supplementation vs placebo or folic acid
2. Multiple micronutrient supplementation vs IFA or iron or other control/placebo

Outcome measures:

1. Survival/mortality: stillbirth, neonatal/perinatal, or infant mortality
2. Birth outcomes: Birthweight (BW), Low birth weight (LBW), preterm, small-for-gestational age (SGA), Large-for-gestational age (LGA)
3. Other outcomes: growth (anthropometry), cognition, long-term health effects

Meta-analysis of Iron/Iron + Folate Supplementation (IFA) on Anemia and Birth Outcomes

- RCT & quasi-RCT
- Prenatal Fe or IFA vs no suppl./placebo
- 30 studies (up to Jun 2011) (quality=moderate)
- Outcomes:
  - maternal: anemia hemorrhage, mortality,
  - Infants: BW, LBW, preterm, perinatal death

Findings: Maternal

Iron vs no intervention/placebo:

- RR 0.31 (0.22, 0.44) for anemia
- RR 0.44 (0.28, 0.68) for IDA

Findings: Infants, Iron vs control/placebo:

- LBW: RR 0.80 (0.71, 0.90)
- BW: Significantly higher BW, mean diff. 42 (95%CI 9.3, 75) g
- NS for SGA, preterm, perinatal mortality

Imdad & Bhutta, Paediatr Perinat Epi 2012

Meta-analyses of Iron-containing Multiple Micronutrient (MMN)* Supplements during Pregnancy

	Fall, et al, 2009	Shah, et al, 2009	Ramakrishnan, et al, 2012
Study design	RCT	RCT & quasi-exp.	RCT
Comparison	MMN (15) vs IFA/Fe	MMN (≥15) vs (≤3) IFA/placebo	
# of trials	12 in LMIC	13 in LMIC + France	16 in LMIC + France
MMN used	UNIMMAP (15 nutrients [30 mg Fe])	Various nutrient combinations [30 or 60 mg Fe]	UNIMMAP (6) & other combinations [30 or 60 mg Fe]
Outcomes	Pregnancy outcomes & perinatal mortality	Pregnancy outcome	Pregnancy outcomes & survival

* Containing iron-folic acid

Results

	Fall, et al, 2009	Shah, et al, 2009	Ramakrishnan, et al, 2012
% LBW	0.89 (0.8, 0.99)	0.83 (0.74, 0.93)	0.86 (0.81, 0.91)
% SGA	0.9 (0.82, 0.99)	0.89 (0.77, 1.01)	0.83 (0.73, 0.95)
% Preterm	1.0 (0.93, 1.09)	0.99 (0.8, 0.99)	0.99 (0.93, 1.03)
Mean diff in BW, g			
% LGA	1.13 (1, 1.28) *	--	--
% Stillbirth	--	--	0.89 (0.8, 0.99)
Neonatal mortality	--	--	0.97 (0.87, 1.09) **
Perinatal mortality	1.11 (0.93, 1.33)	--	--

*BW increased more in mothers with high BMI

**Significance if supplemented after 12 wks, RR 1.38 (1.05, 1.81)

Meta-analysis of Multiple Micronutrient (MMN) Supplement and Subgroup Analysis

	Haider & Bhutta, Cochrane rev 2017	Smith, et al, Lancet GH 2017
Study design	RCT (high quality study)	RCT (high quality study) (individual level data)
Comparison	MMN vs IFA/Fe	MMN vs IFA
# of trials	17 (15 in LMIC)	17 in LMIC
MMN used	Various nutrient combinations [30 or 60 mg Fe]	Various nutrient combinations [30 or 60 mg Fe]
Outcomes	Birth outcomes & survival	Birth outcome & survival
Subgroup analysis	Maternal height, BMI, time of suppl, iron dose	At trial entry (GA, mat. age, BMI, stature), mat. ed., adherence to supp,

Results

	Haider & Bhutta, Cochrane rev 2017	Smith, et al, Lancet GH 2017
% LBW	0.88 (0.85, 0.91)	0.86 (0.81, 0.92)
% SGA	0.92 (0.86, 0.98)	0.94 (0.90, 0.98)
% Preterm	0.96 (0.9, 1.03)	0.93 (0.87, 0.98)
% Stillbirth	0.97 (0.87, 1.09)	0.97 (0.85, 1.11)
Neonatal mortality	1.06 (0.92, 1.22)	0.99 (0.89, 1.09)
Perinatal mortality	1.01 (0.91, 1.13)	--
6 mo mortality	--	0.93 (0.86, 1.00)
Infant mortality (≤1 y)	--	0.97 (0.88, 1.06)

Effect Modifiers in Subgroup Analyses (Smith, et al, 2017)

Survival benefits: MMN

1. Significantly reduced risk of neonatal mortality (15%) and mortality at 6 mo (15%) & 1y (20%) among females
2. Significant higher reduction in 6 mo mortality (29 vs 7%) among anemic pregnant
3. Significant reduction of risk of still birth, 6 mo & 1y mortality among infants born to mothers with high adherence to supplement (≥ 95%)

Livebirths:

1. Significantly reduced risk of LBW and SGA among anemic mothers
2. Maternal underwt (BMI ≤18.5) had greater reduced risk of preterm while mothers with higher BMI (>18.5) had greater increased risk of LGA
3. GA started supplement: before 20 wks, greater reduced risk of preterm; ≥ 20 wks, greater reduced risk of SGA

Summary

- Meta-analysis showed consistent benefits of MMN over IFA for survival and birth outcomes.
- Maternal anemia, underweight, high adherence to supplement and female infants are significant effect modifiers.

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Benefits vs Risks

1. Iron deficiency and supplementation in **Hemoglobinopathy** (abnormal Hb carriers)
2. Iron supplementation and **infection** and growth in infants

Hemoglobinopathy in Asia

- Hemoglobinopathy/thalassemia carriers are **highly prevalent** in several countries in SEA, southern China, and parts of SA and Pacific islands
  - HbE is 30-40% in Thailand, Cambodia, Laos
  - α- thalassemia 1-30% in SE Asia
- **Misperception** that iron intervention causes iron overload
- **Withholding iron** to women during pregnancy or anemia in thalassemia carriers, leaving ID/IDA untreated or prevented

Using Stable Isotope to Assess Iron Absorption and Incorporation into Hb

- Reproductive age women: normal Hb and thalassemia carriers
- Fe-fortified diet (3 mg Fe/meal), iron absorption and utilization in HbAE are not significantly different from normal Hb
- α-thal and ß-thal traits absorbed more iron and utilized less, but not overload as indicated by S. ferritin

	Normal Hb	HbE trait	α-thal 1 trait	ß-thal trait	HbE/ß thal
Fractional Fe absorption, %	3.0 (0.3, 5.8) [a]	4.0 (-4.6, 12.6) [ab]	6.3 (1.9, 10.8)[b]	6.6 (-4.2, 15.9) [b]	>100[c]
Erythrocyte Fe incorporation, %	93 (83, 104)[a]	90 (80, 101) [ab]	79 (68, 89) [bc]	80 (70, 90)[cd]	21.2 (9, 33)[d]

Zimmermann, et al, AJCN 2008

Iron Supplementation During Pregnancy: Normal (HbAA) vs Carrier (HbAE)

- Daily iron supplementation (120-240 mg) from mid-pregnancy till delivery
- Normal HbAA: Hb responses is larger and inversely by initial Hb level
- HbE carriers similarly responded, but maybe smaller in homozygous E
- No adverse effect (iron overload)
- Side effects (nausea, vomiting): higher when high iron doses were used. No difference between normal Hb & carriers.

Charoenlarp, et al, AJCN 1988;
Sanchaisuriya, et al, AJCN 2007

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Benefit & Risk of Iron Supplementation in Infants & Young Children

Prevalence of anemia is very high in infants in many LMIC

Iron deficiency resulted in anemia and possibly irreversible neurodevelopment

Iron supplement is recommended for treatment of anemia

Benefits and potential adversity (esp. areas with high infection and malaria) and growth have been reported

Iron and Infection Interaction

- Acute phase response to infection, increased hepcidin results in downregulation of iron absorption, and sequestration from macrophage– reduced plasma iron, so impaired bacterial growth
- Iron supplementation – increased TS, beyond binding capacity – NTBI for virulent pathogens
- Conflicting evidence from meta-analysis of iron supplementation in children:
  - Gera & Sachdev (2002) found no overall increase in infections, except risk of diarrhea
  - Oppenheimer (2001) found increased risk of clinical malaria in malaria endemic area
- A large trial in highly endemic area of malaria (Pemba), iron group had 15% increased risk of death and 11% of hospitalization (Sazawal, et al, 2006)
- In non endemic area in Nepal, iron supplementation decreased anemia without increases in risk of death, diarrhea or respiratory tract infection (Tielsch , et al, 2006)

Recent Meta-analysis

Cochrane review (Neuberger, et al, 2016) showed no overall clinical risk of malaria, but increased risk (16%) if given with no malaria prevention.

Unabsorbed iron from micronutrient powder increased risk of intestinal colonization by pathogens – leads to increased diarrhea (Jaeggi, et al, 2014; Soofi, et al 2013).

In contrast, iron supplementation did not increase risk of malaria in pregnant women in malaria endemic areas, possibly due to more developed host immunity.

Iron Supplementation (IS) and Growth in Children

- A few studies showed negative impact of iron supplementation on growth in iron replete young children
  - IS to 12-18 mo. Indonesian children had significantly lower weight gain in iron group; improved in iron deficient (Idjradinata, et al, 1994)
  - IS had negative effect on length gain in 4-9 mo. non-anemic infants in Hondurus and Sweden (Dewey, et al, 2002)
  - IS to iron replete (2 mg/kg/d) vs iron deficient (6 mg/kg/d) 6-24 mo. children, found significant decreases in weight and length gains in iron replete children (Majumder, et al, 2003)
  - Significant negative effect on weight gain in iron replete 6-12 mo. infants (Lind, et al, 2008)

Meta-analysis on Iron Supplement in 4-23 mo. old Children

- 35 trials: Iron supplements vs no Fe/placebo:

Benefits

1. reduced risks of anemia (RR 0.61 [0.5, 0.74]), ID (RR 0.3 [0.15, 0.6] and IDA (RR 0.14 [0.1, 0.22]
2. Child development, non-significant mean difference in mental scores (1.65 [-.63, 3.94] and psychomotor (1.05 [-1.36, 3.46]
3. No significance in anthropometry (final weight, WAZ, length, LAZ)

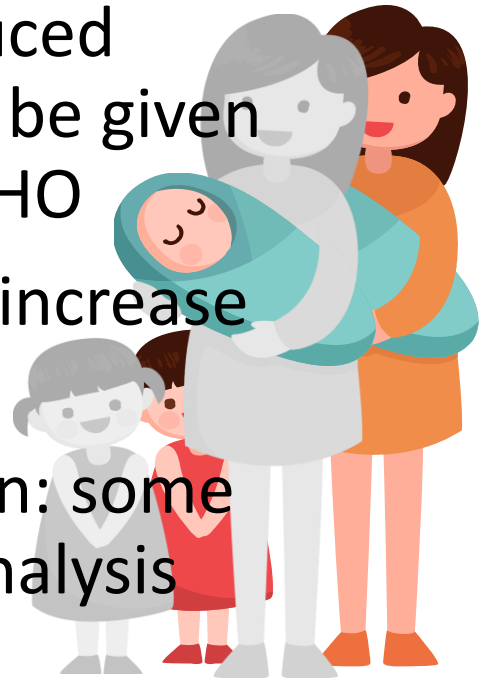
Possible adversity

- Children in iron group had lesser length and weight gains
- Increased vomiting (side effects) RR 1.38 (1.1, 1.73)
- Increased fever RR 1.16 (1.02, 1.31)

Pasricha, et al Lancet GH 2013

Summary

1. Iron intervention is safe and beneficial for thalassemia carriers. More systematic documentation of possible adversity when high dose iron is given for a long duration such as during pregnancy
2. Iron supplementation in infants improved iron status/reduced anemia (benefits), but in malaria endemic areas, it should be given with malaria preventive measures as recommended by WHO
3. In non-malaria endemic areas, iron supplementation may increase the risk of common illnesses, namely, diarrhea and fever
4. Negative effects on weight and/or length gains in uncertain: some reported in iron replete infants, no evidence from meta-analysis



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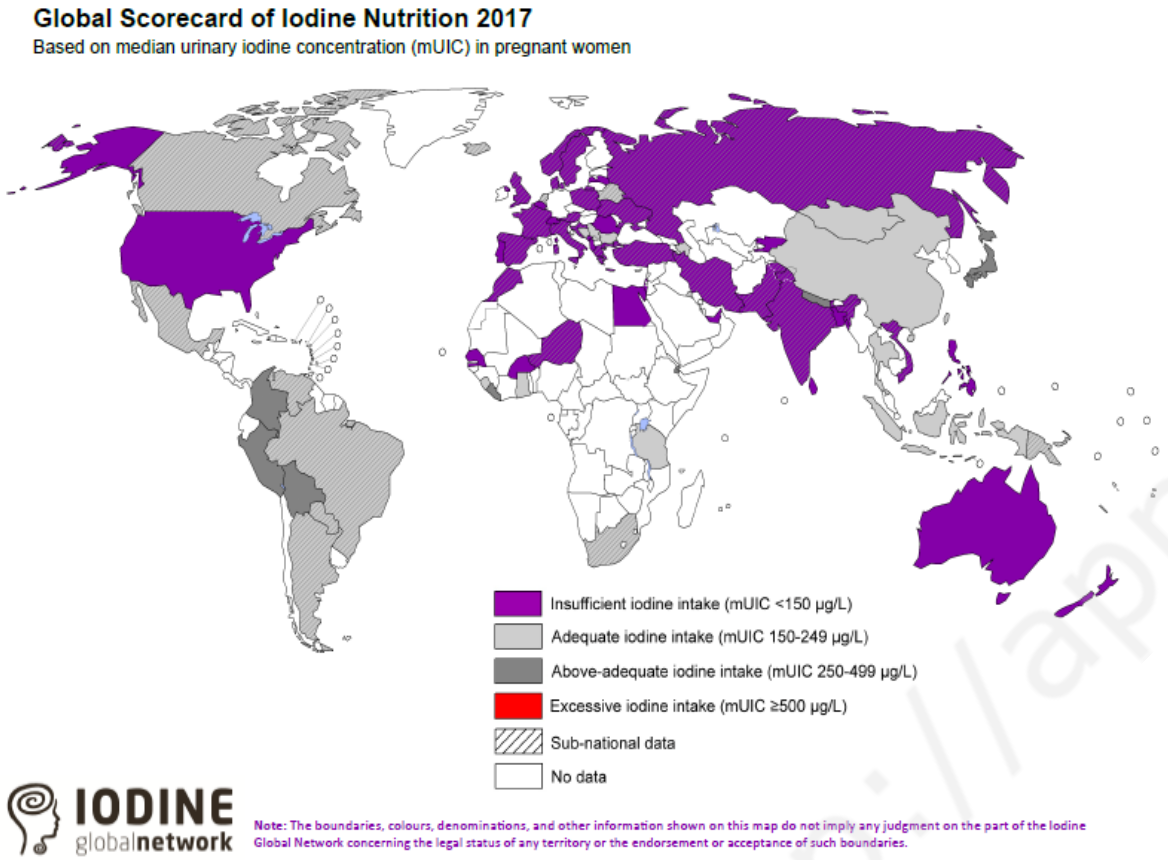
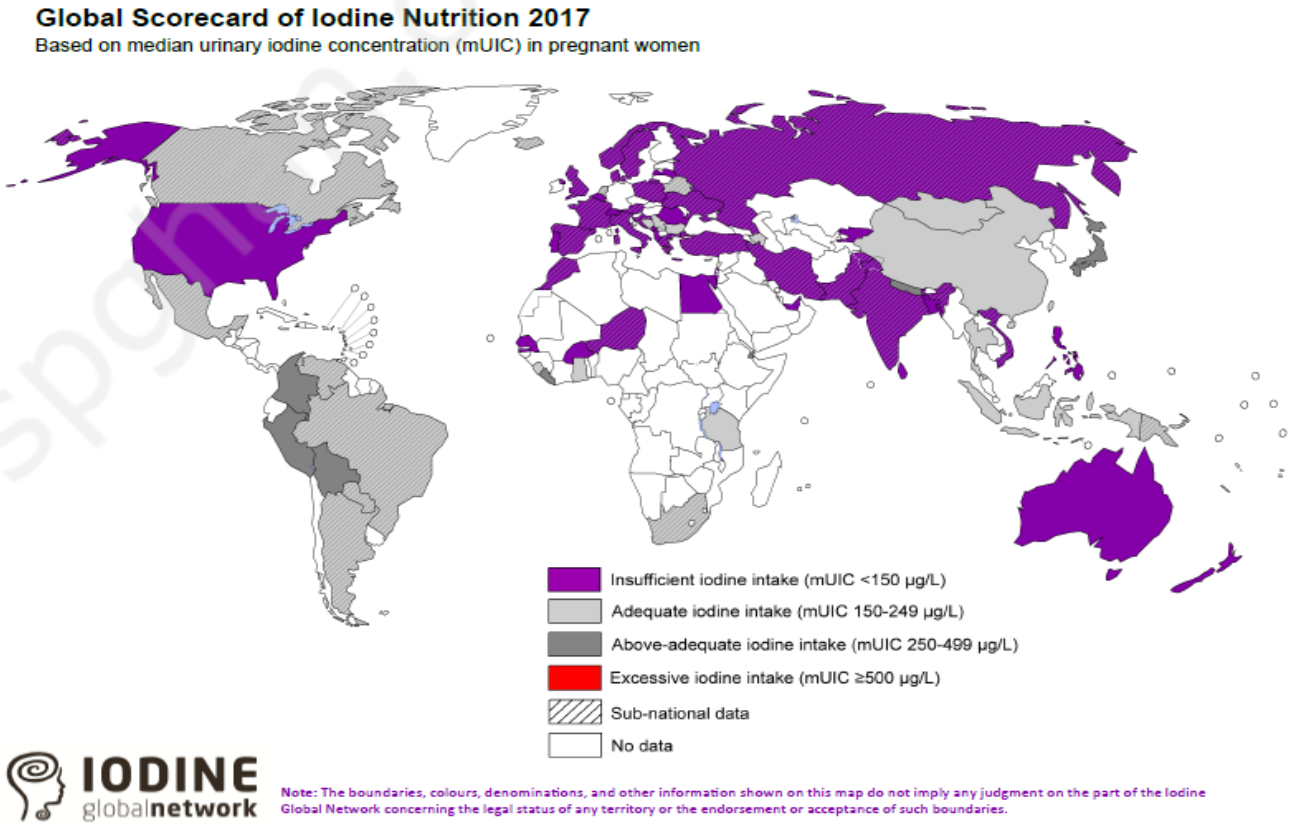
SAC & All Population



Pregnant Women



108 countries with mandatory legislation for salt iodization

WHO/UNICEF Statement 2007

- In areas of **moderate and severe iodine deficiency** (median urinary iodine <50 ug/L or total goitre rate more than 20%), the objective should be to **provide additional iodine as a supplement** to all pregnant & lactating women at daily dose 250 µg/d or 400 mg/y iodized oil.
- It is unclear, in **mild-moderate iodine deficient** pregnant population, whether iodine supplementation will be needed or not.

Studies on iodine supplementation in mild-to-moderate iodine deficiency during pregnancy

- RCT, provided 120-250 µg I/d
  - small sample size
  - only assessed thyroid functions during pregnancy or newborn
  - no follow-up on babies on iodine status, cognitive development
- Only observational studies reported cognitive assessment

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Maternal Iodine supplementation and effects on Thyroid functions and CHild development: MITCH

Objective:

- To determine effects of daily oral dose of 200 µg iodine vs placebo to mild-to-moderate ID pregnant women on neurodevelopment of offspring at 1,2 and 5 y

Study site:

- Thailand: Obstetrics and Gynecology Dept, Ramathibodi hospital, Mahidol U, Bangkok, Thailand; India: Obstetrics and Gynecology Dept, St Martha's hospital, Bangalore, India (in collaboration with ETH, Zurich, Switzerland & Wageningen University, the Netherlands)

Ethical approval:

- Human Ethics Committee, Mahidol University, Thailand & St John's Research Institute, india, Ethical Committee, Wageningen University,

  the Netherlands

- ClinicalTrials.gov identifier: NCT00791466

Gowachirapant et al, Lancet Diabetes Endocrinol 2017

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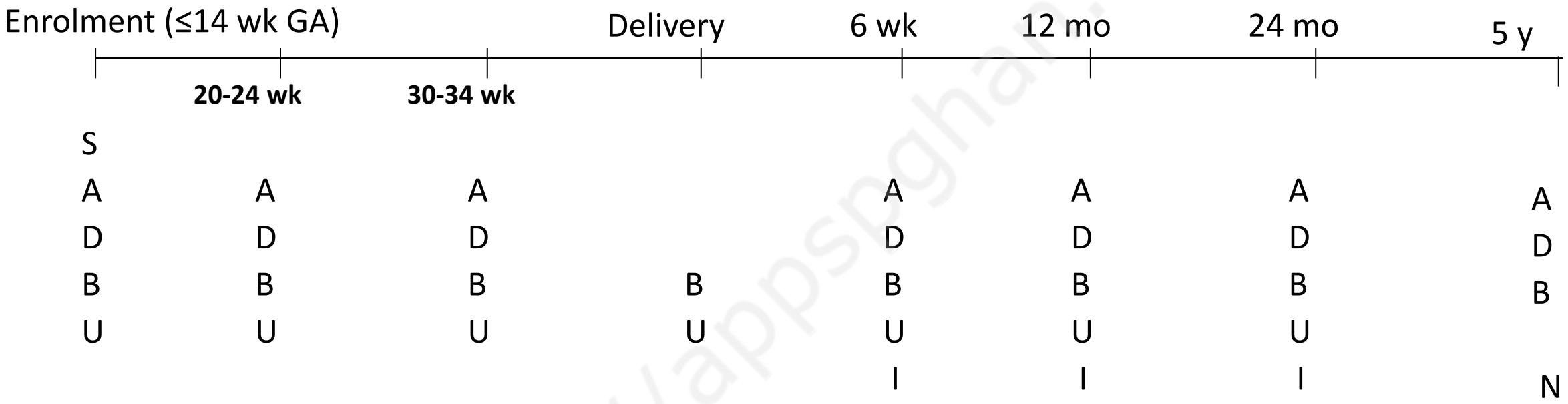
STUDY PROTOCOL



S = Socio-demographic information **A = Anthropometric measurement**

D = Dietary assessment **U = Ultrasound (thyroid volume)**

B = Biological samples (thyroid function [TSH, Tg, TT3, TT4, fT4, fT3, TPO-Ab] and iodine nutrition [UIC]) **I = Infant growth and development (NBAS, Bayley's scales at 1,2 y)**

N = Neurodevelopment at 5 y follow up (WPPS, Brief-P & SDQ)

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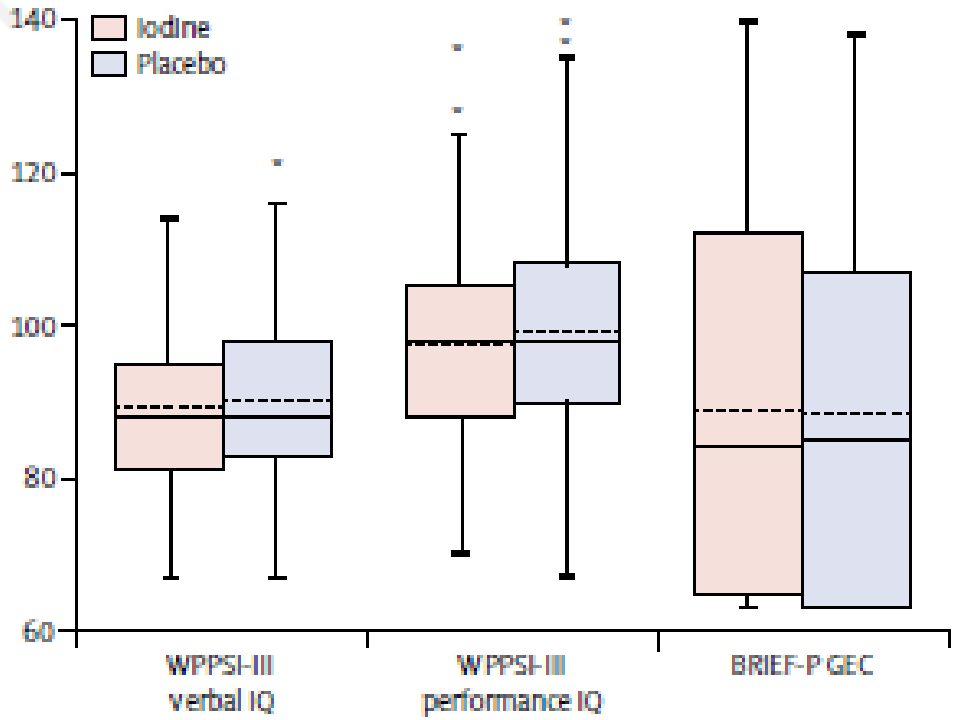
UIC During Pregnancy & Postpartum

UIC (ug/L)	Iodine		Placebo	
1st trimester	**404**	**135** (80, 219)	**409**	**125** (81, 210)
2nd trimester	**291**	**231** (131, 365)	**274**	**174** (92, 284)
3rd trimester	**280**	**247** (140, 349)	**299**	**159** (105, 252)
P-value *	**<.0001**			
6 wk postpartum	**217**	**119** (73, 186)	**218**	**112** (63, 194)
P-value **	**0.61**			

*repeated measure adjusted HH income, mat. Ed, BMI at entry
**testing difference controlling HH income, mat. Ed, BMI at entry

Birth Outcomes & Neurodevelopment

- % Preterm: Iodine vs placebo (7 vs 9%)
- % Low birthweight: Iodine vs placebo (12 vs 11%)
- High newborn TSH: Iodine vs placebo (1 vs 2)
- Neonatal Behavior Assessment (NBAS) at 6 wks
- BSID-III at 1 and 2 y
- At 5.4 y, no significant differences in
  - growth, UIC and thyroid functions
  - WPPS-II, BRIEF-P, Strength & difficulty questionnaire



* Data points beyond 1.5xIQR

Gowachirapant et al, Lancet Diabetes Endocrinol 2017

Summary

- In mildly IDD pregnant women:
  - In areas with mild-to-moderate iodine deficiency during pregnancy, iodine supplementation did not confer any benefit on neurodevelopment or growth of offspring at 5.4 y, although it improved maternal iodine intake during gestation.
  - lower TSH and Tg in the iodine group – placebo group slightly increased thyroid activity to compensate for low iodine intake.

Overall Conclusion

- Evidence on benefits of MMN supplement during pregnancy are important; current WHO recommendation on prenatal IFA needs to be reviewed, in light of accelerating the achievement of key WHA targets for maternal and child nutrition.
- Programmatically, however, there are continued needs to improve adherence to supplementation and health services to ensure adequate care during prenatal services and at child birth.

Multiple Micronutrient Supplementation During Pregnancy

Overall Conclusion

Benefits and Risk of Iron Supplementation

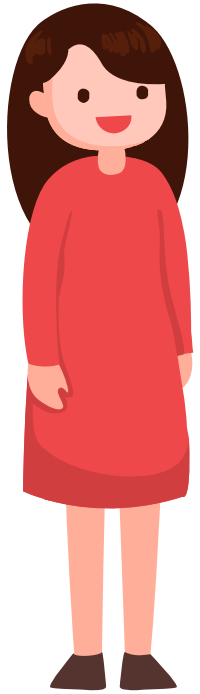
- Population having high prevalence of abnormal Hb carriers, iron intervention is safe and responsive to correct ID/IDA
- In infants, iron and infection could result in high morbidity and death, especially, in malaria-endemic areas. WHO recommend measures to prevent/control infection alongside to avoid serious adversity
- Risk on growth in iron replete infants needs further confirmation

Iodine Supplement in Mild-to-moderate IDD during Pregnancy

- Iodine supplementation during pregnancy may not be needed, provided that iodization program is effective (coverage and quality) and efforts be given on monitoring of USI and urinary iodine in children and if possible, in reproductive age/pregnant women

Take Home Message

- High dose micronutrient supplementation during pregnancy and young childhood has been the mainstay nutrition intervention in LMIC, including Asia.
- Supplementation may be needed for some target groups; benefits vs risks be carefully considered. Other concurrent intervention may be necessary (e.g., malaria management, WASH), or targeted supplementation be considered.
- The declines of prevalence & severity of micronutrient deficiencies in many LMIC in Asia are noted; more attention and efforts should be given to promoting dietary approach with effective nutrition education/counseling for sustainability.



Thank you for your attention!

Acknowledgement: Thanit Vinitchagoon for assistance on slide presentation