IHME

Simulation Finds Antenatal Intravenous Iron Reduces Anemia Burden Related to Pregnancy and Impacts Under 5 Mortality

The Vivarium Framework

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Gender inclusive language

- For this presentation, we would like to start by acknowledging that not all people who can get pregnant and give birth are cis-gendered women, and our team would like to be more inclusive to all sexes and genders in our language

- The majority of the input data used includes an undifferentiated sex/gender category, which is created from a composite of studies that define sex and/or gender in a multitude of ways

- We acknowledge that creating a model based on this data leads to limitations in our analysis; however, for this talk, we will choose to use gender inclusive terms throughout the presentation

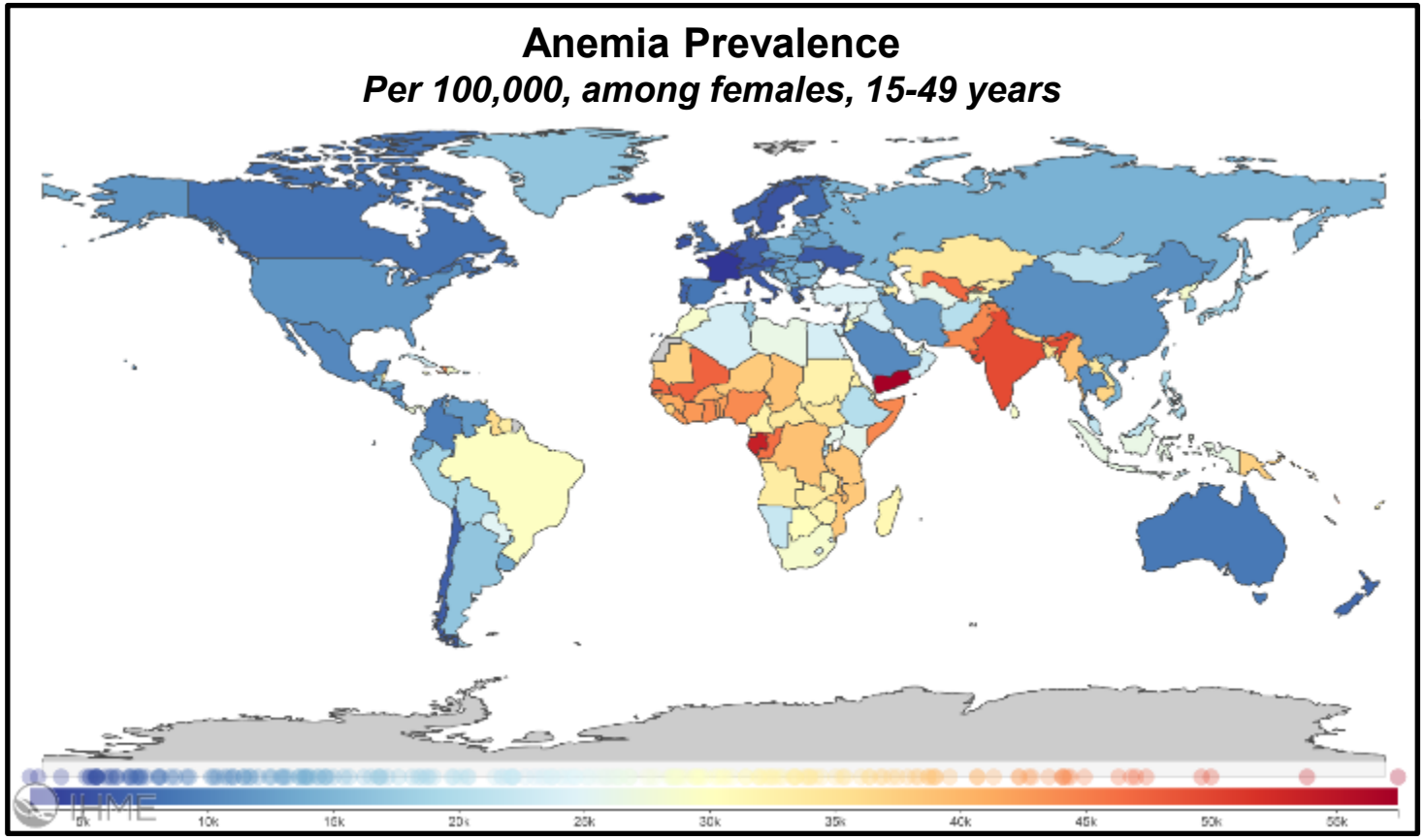
- A dictionary:
  - Maternal health → pregnancy related health
  - Maternal disorders → pregnancy related disorders
  - Maternal mortality → pregnancy related mortality
  - Women of reproductive age → women and birthing people of reproductive age
  - Pregnant and lactating women → pregnant and lactating people

Outline

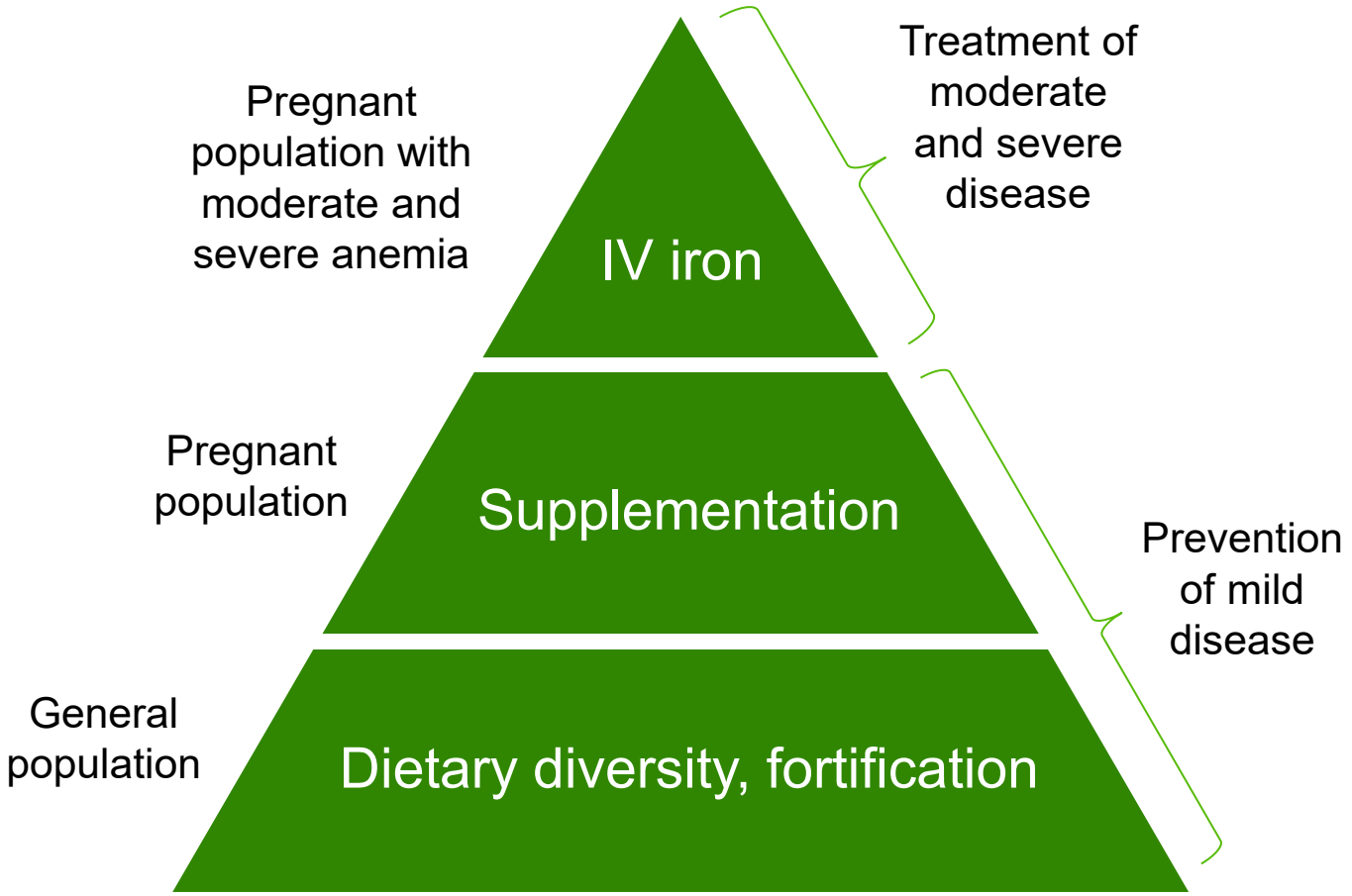
- **Introduction**
- Overview of Simulation
  - Vivarium Framework
  - GBD Data
  - Uncertainty Measurements
  - Parent/Child Dyads
- Results
  - Pregnancy Related Outcomes
  - Child Outcomes
  - Costs
- Questions

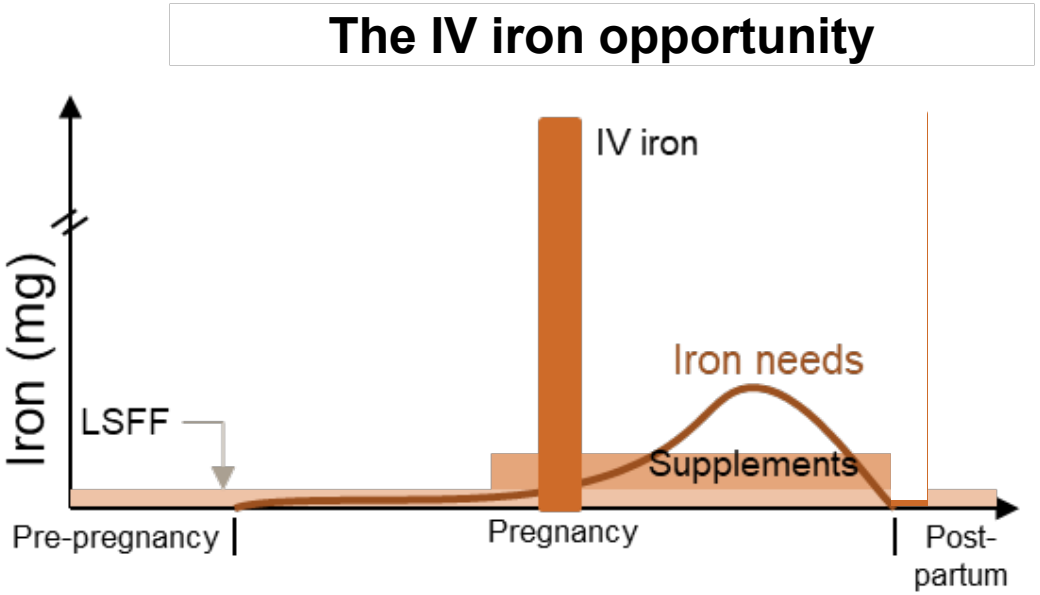
Introduction

- Pregnancy related and neonatal disorders were a leading cause of DALYs, representing 15% of total population DALYs, in Sub-Saharan Africa according to GBD 2019
- Because of this, there is a lot of effort and attention on addressing unmet needs and finding effective interventions
- Trials remain costly, and results can be highly localized in nature
- Simulation studies are useful to evaluate the possible impact of interventions across regions
- Today, we will look at the impact of IV Iron on pregnancy, and neonatal health in Sub-Saharan Africa and South Asia



Addressing anemia throughout pregnancy

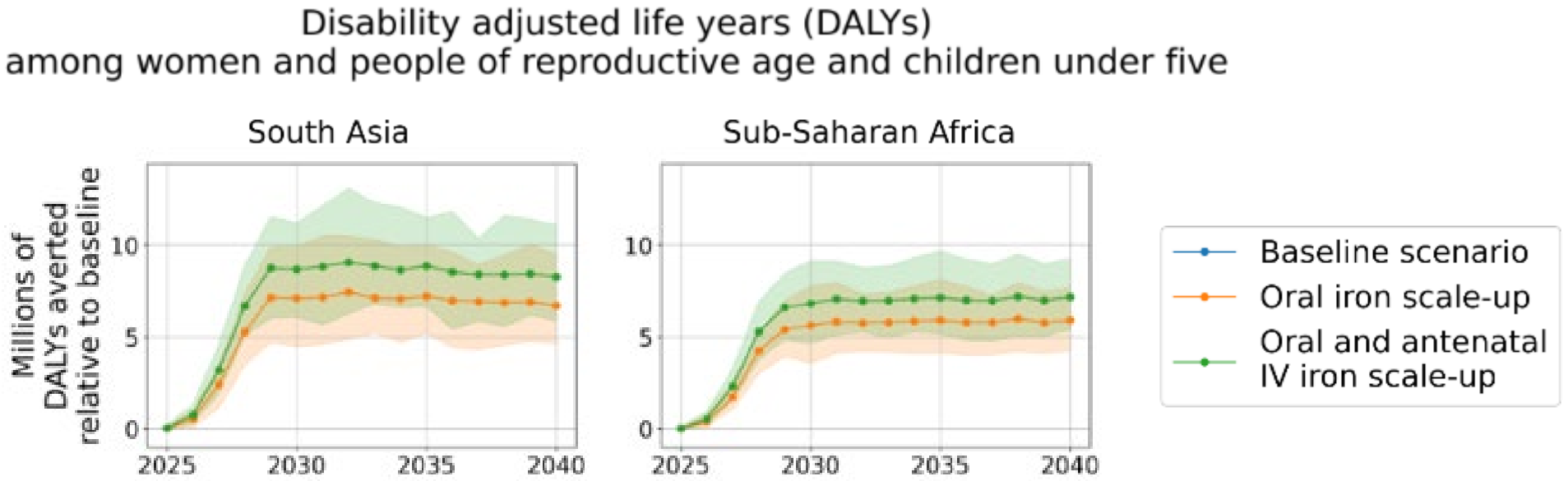




High Level Results

Simulated three scenarios

- Baseline
- Oral iron scale-up
- Oral iron and antenatal IV iron scale-up



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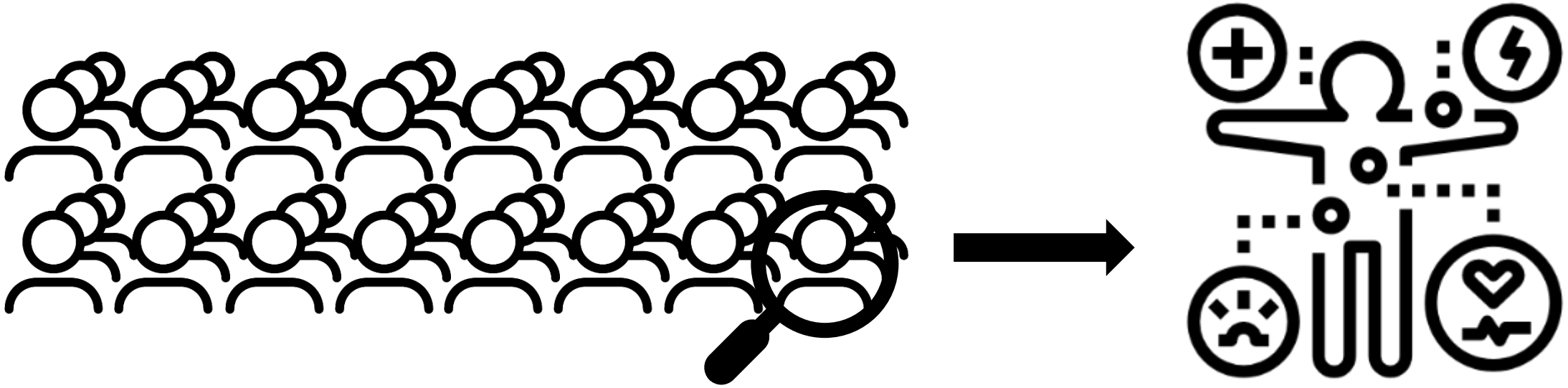
Microsimulation overview



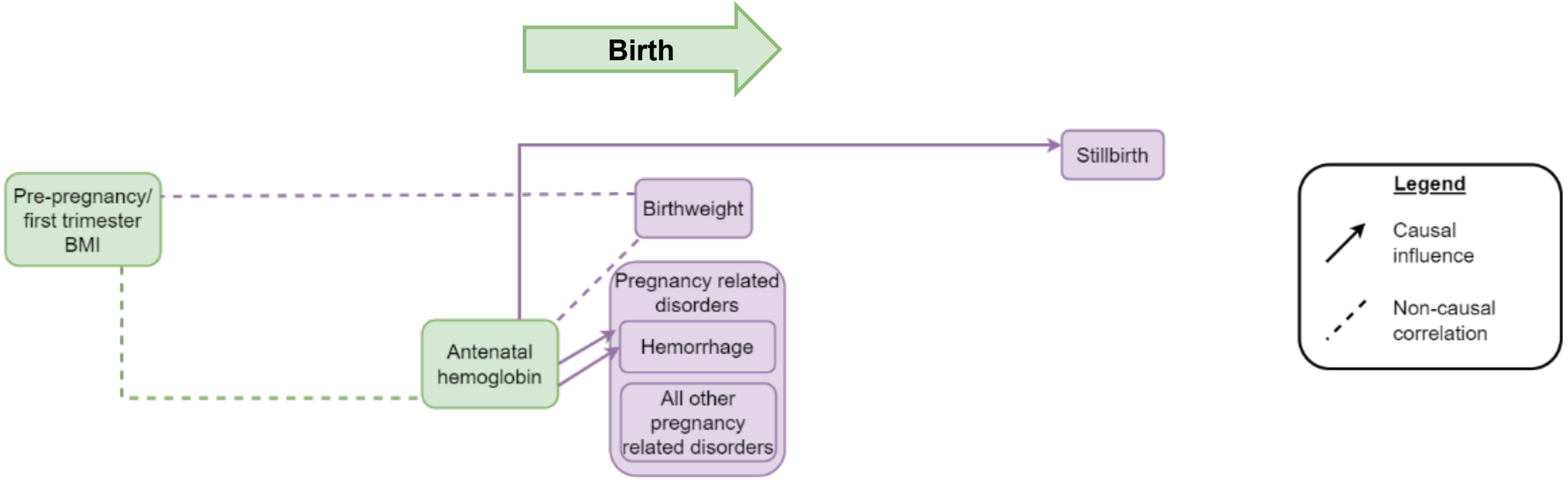
At the population level, data is **calibrated to match estimates from IHME's Global Burden of Disease** databases or other sources

Microsimulation allows us to assign **heterogeneous attributes to individual** simulants, allowing more **flexibility** compared to a compartmental model

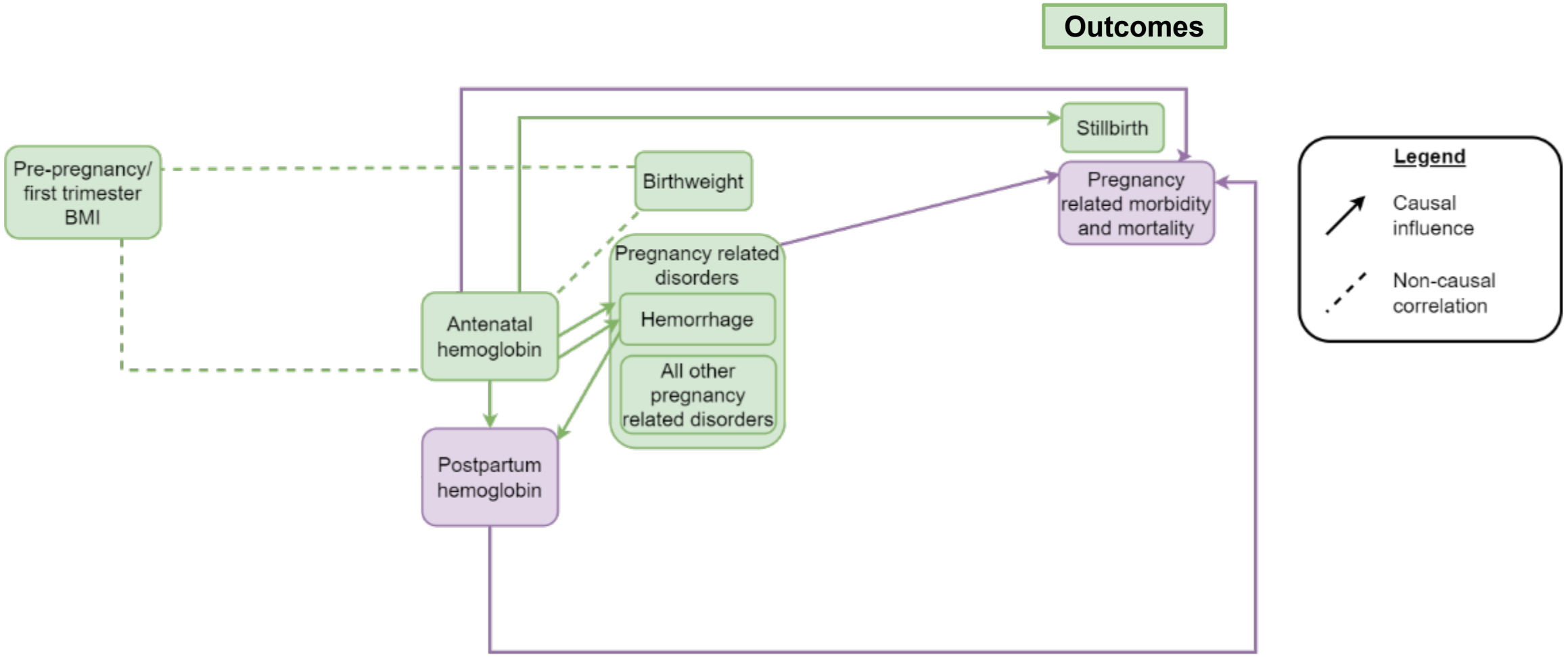
Simulants experience disease, treatment, morbidity and mortality and rates correlated with their attributes

IV iron simulation concept model diagram

IV iron simulation concept model diagram



IV iron simulation concept model diagram



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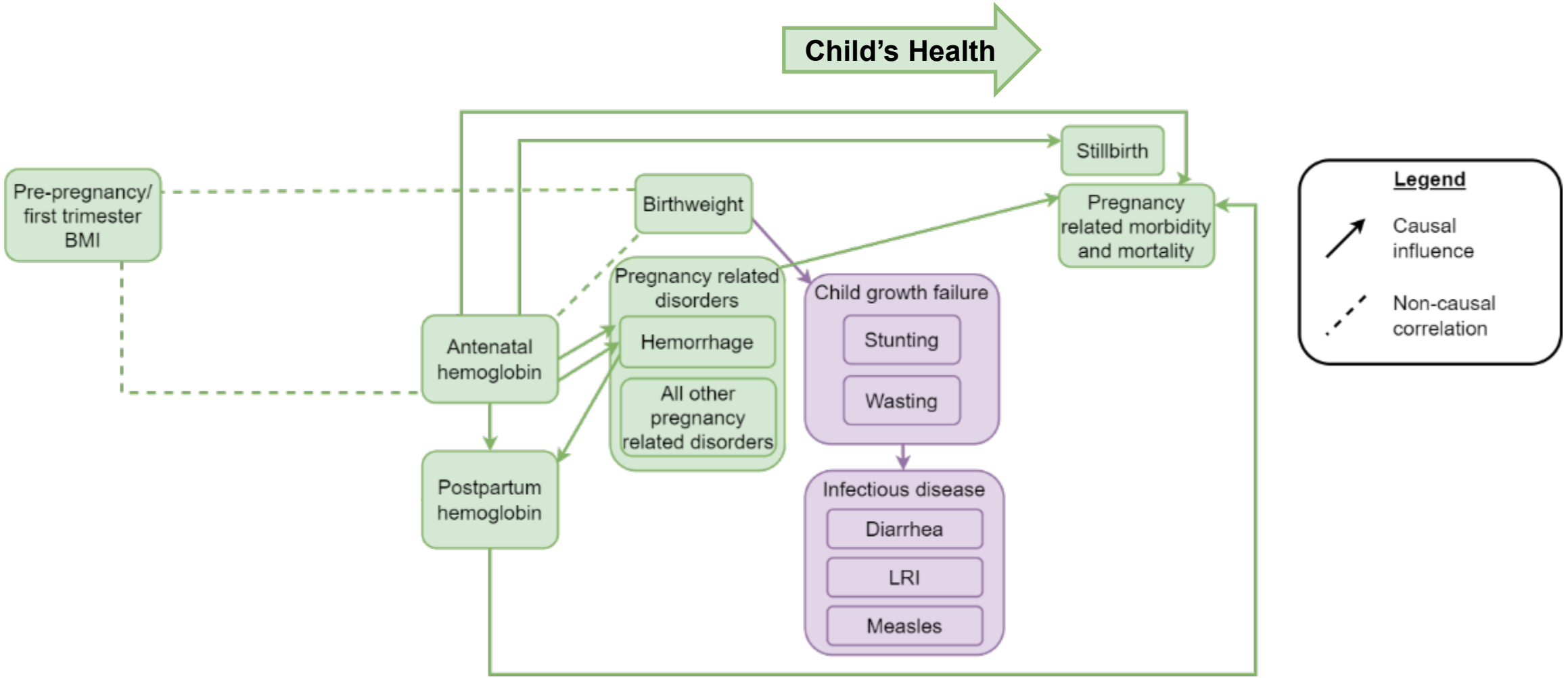

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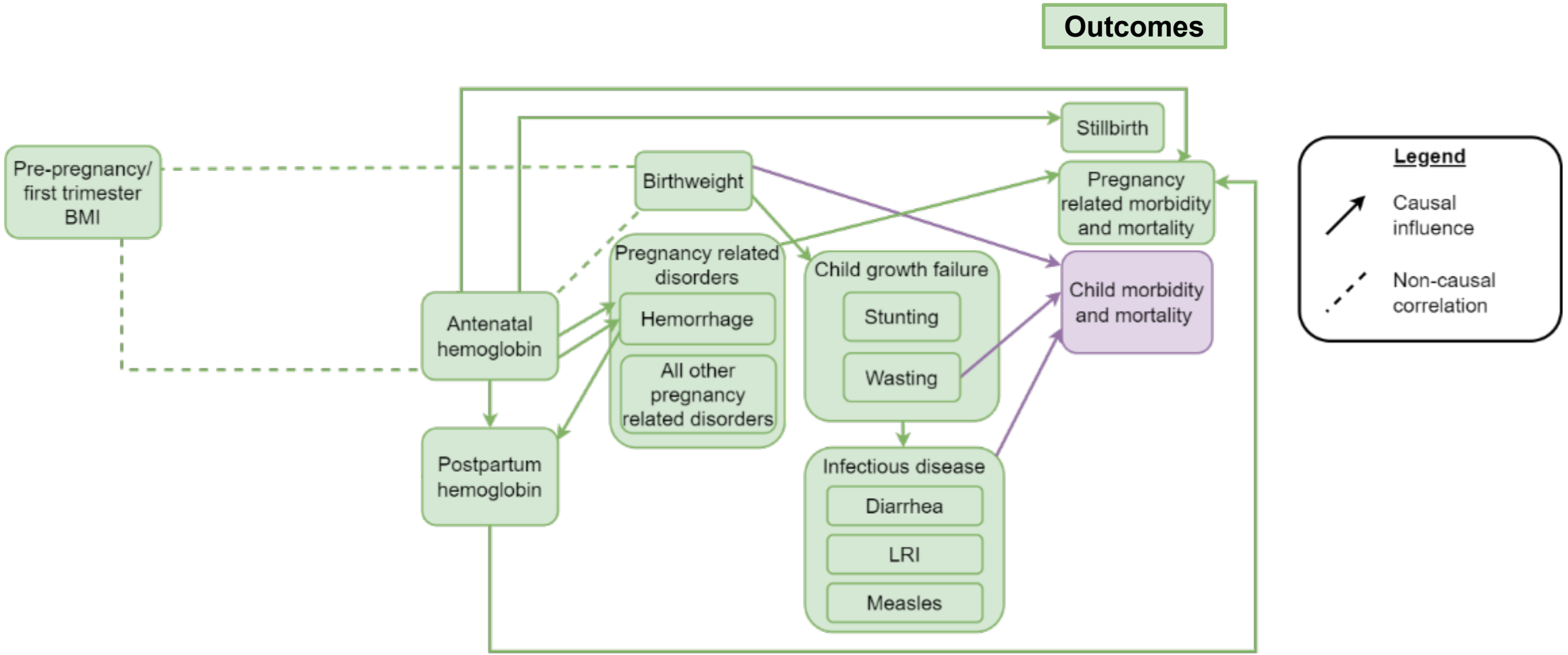

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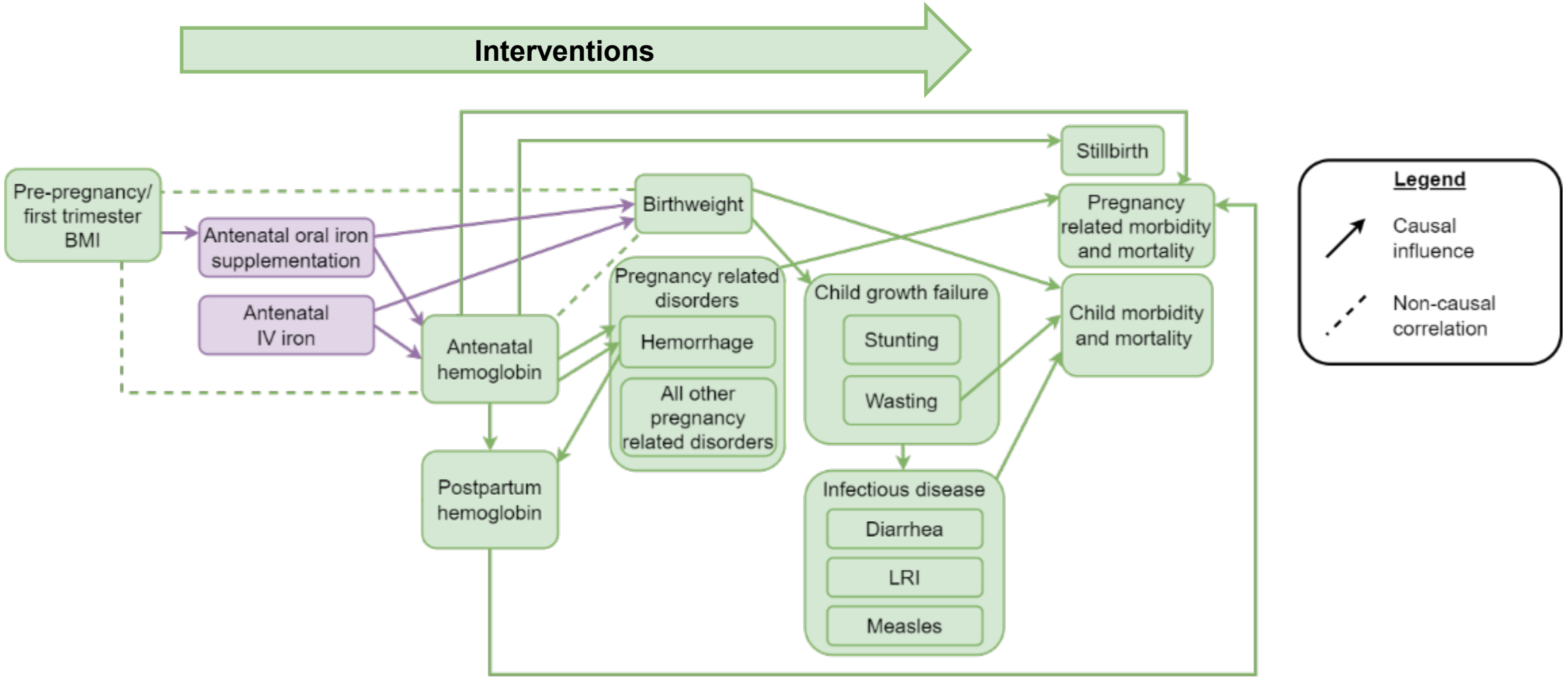

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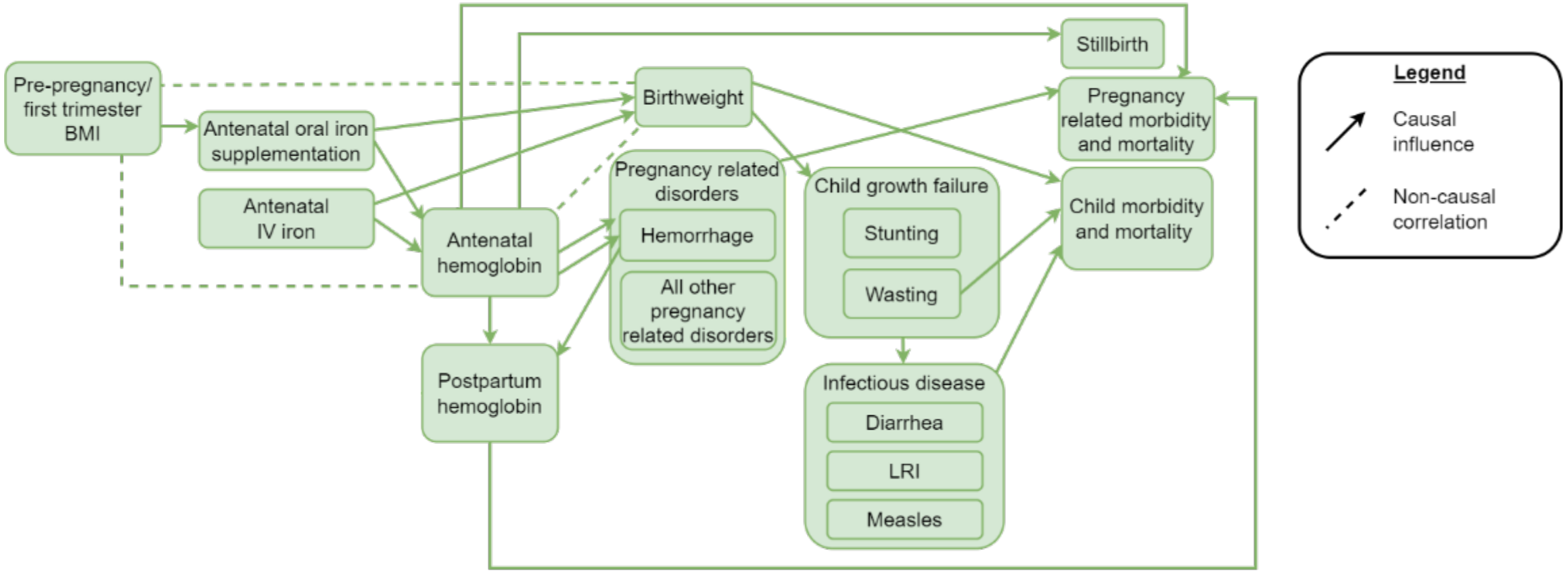
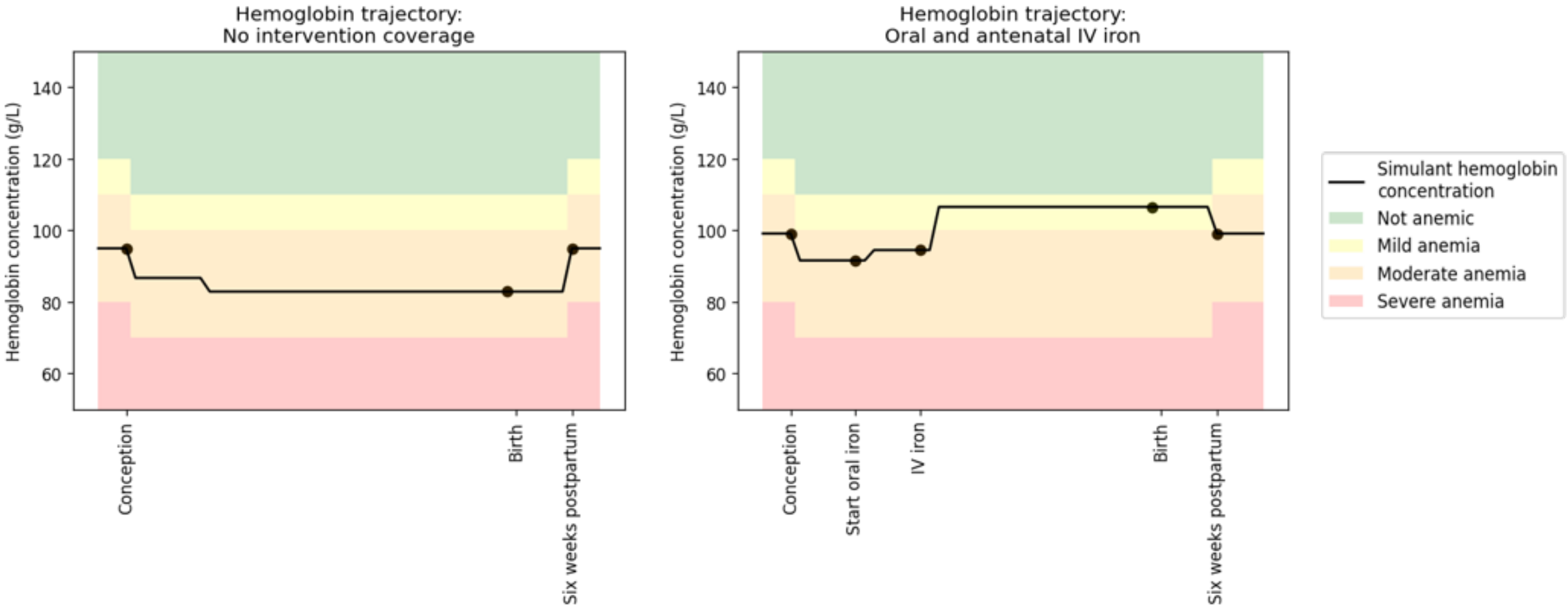


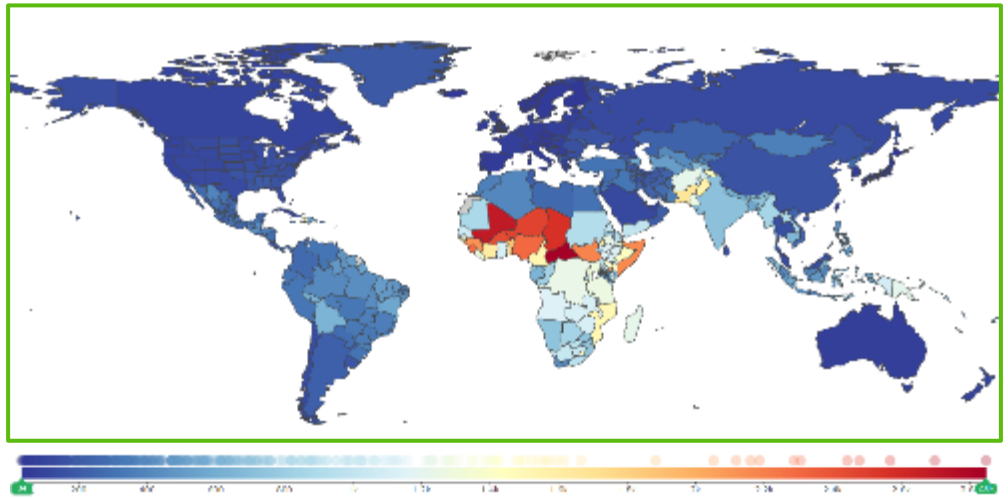
Hemoglobin trajectory plot



Framing: IHME and the Global Burden of Disease Study (GBD)

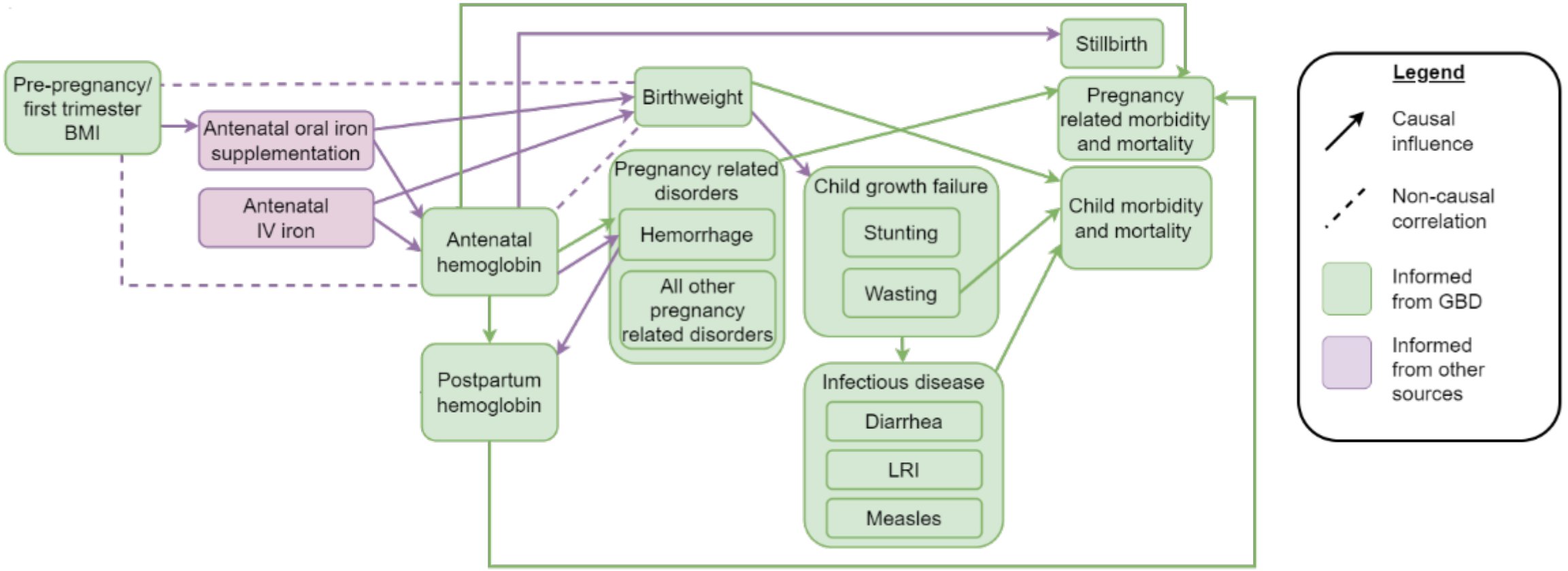
- The Institute for Health Metrics and Evaluation (IHME) runs the Global Burden of Disease (GBD) collaboration, which houses the world's most comprehensive collection of data on disease risks, incidence, prevalence, morbidity, and mortality
  - Age-, sex-, year-, and location-specific estimates for 900+ locations globally

Data sourced from over 120,000 datasets covering 195 countries



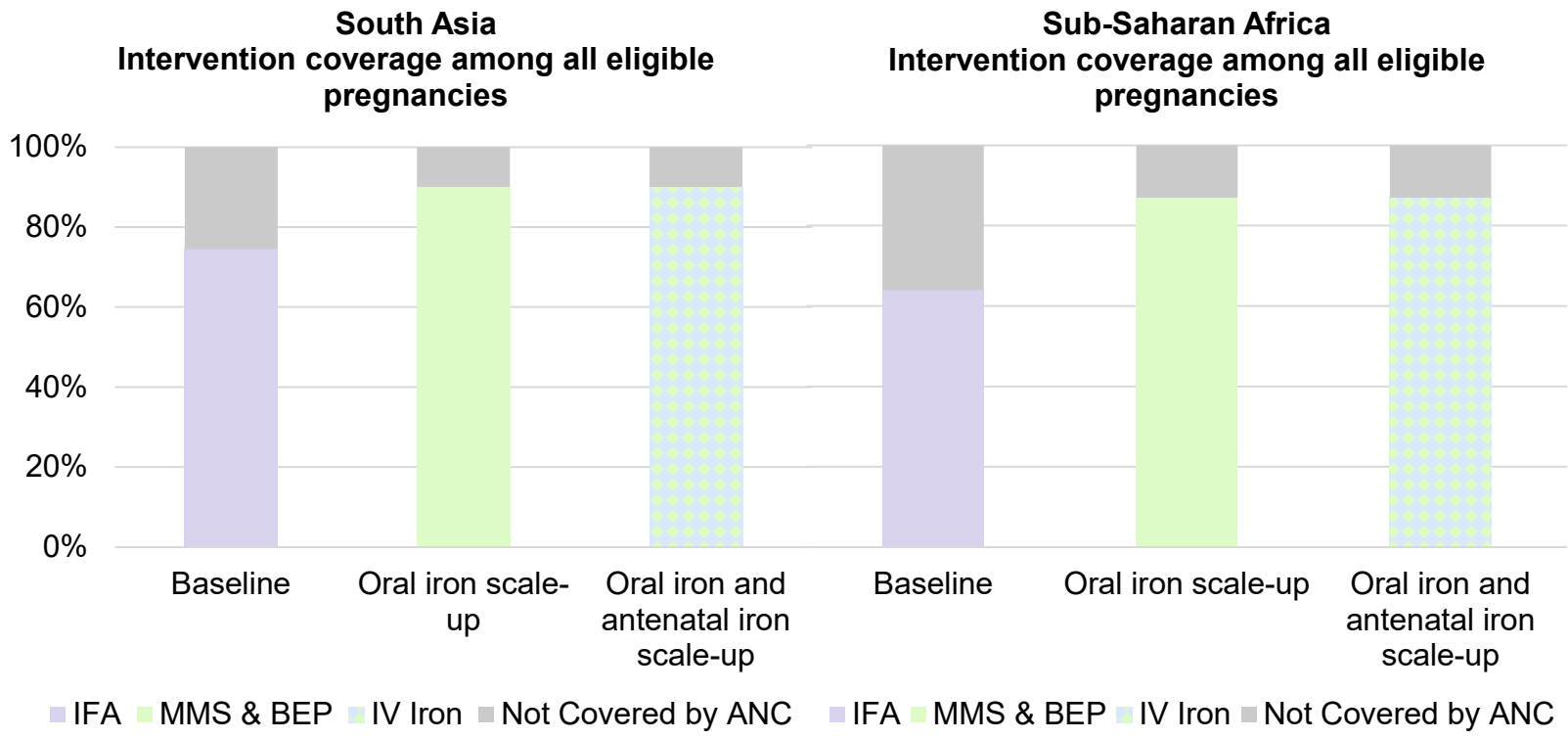
Under-5 deaths per 100,000 person-years

IV iron simulation concept model diagram: Data sources



Simulated scenarios

Scenario	Intervention	Target population
Baseline	Iron folic acid supplementation (IFA)	All pregnancies
Oral Iron Scale-Up	Multi-micronutrient supplementation (MMS)	Pre-pregnancy BMI > 18.5
	Balanced energy protein supplementation (BEP)	Pre-pregnancy BMI ≤ 18.5
Oral Iron Scale-Up and Antenatal IV Iron	Antenatal IV iron	Hemoglobin ≤10 g/dL in 2nd/3rd trimester

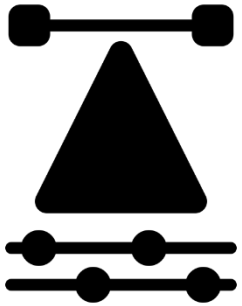


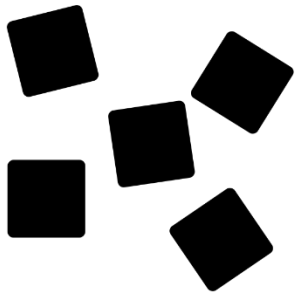
Intervention effects

Intervention	Relative to	Birthweight mean difference in grams (95% CI)	Antenatal hemoglobin mean difference in g/L (95% CI)
IFA	No iron in pregnancy	+57.73 (7.66 to 107.79) (Peña-Rosas et al., 2015)[2]	+7.8 (4.08, 11.52)
MMS	IFA	+45.16 (32.31 to 58.02) Meta-analysis of 13 studies from Keats et al., 2019,[3] published in Young et al., 2020[1]	+0
BEP	MMS	+66.96 (13.13, 120.78) (Ota et al., 2015)[4]	+0
Antenatal IV iron	No antenatal IV iron	+50	+23 (SD: 14), normal distribution rectified at zero

- Assume that the effect on hemoglobin occurs two weeks after administration and persist until six weeks postpartum
- Data from BMGF trials/optimistic target profiles unless otherwise stated

Uncertainty Measures

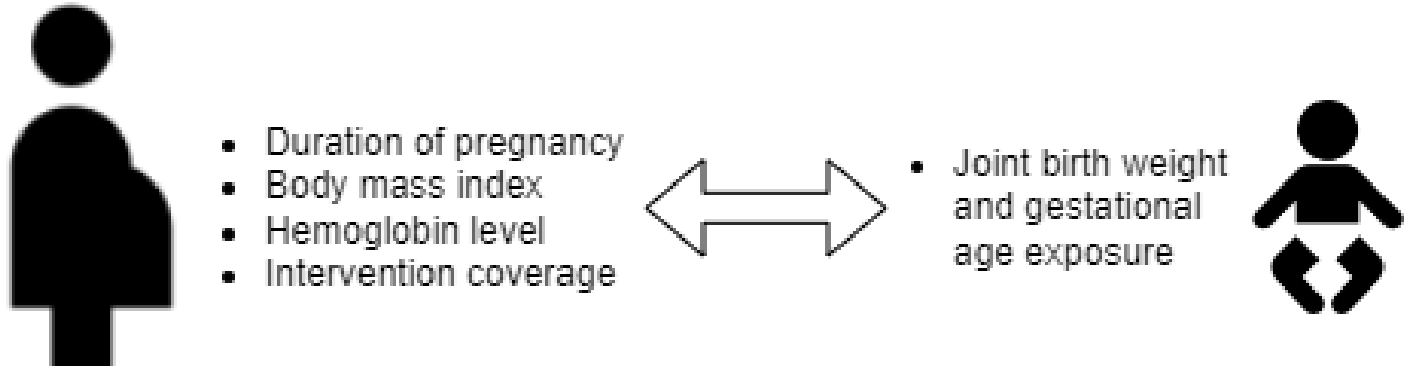




	Heterogeneity	Parameter Uncertainty	Stochastic Uncertainty
Definition	Individual level heterogeneity in risk factors and outcomes, stratified by age and sex. Data is not assumed to be normally distributed but matches the distribution found in the population	Parameter values are rarely preciously known. Therefore, we include 50 draws, provided by GBD data that account for parameter uncertainty	Individual-level events provide stochastic uncertainty in the model, showing what is be due to random chance and what is due to changing inputs
Model Context	Hemoglobin and BMI levels match the population but vary between simulants	The “true” anemia prevalence is unknown, so 50 different possible values were used, and results calculated with each input	If two identical simulants give birth, one might have a maternal disorder and the other might not due to random chance

Simulated parent-child dyads

- Pregnancy model among women and people of reproductive age
  - Utilizes GBD estimates of ectopic pregnancies, abortion/miscarriage, stillbirths, and live births
  - Current model utilizes crude age-specific pregnancy rates
    - Assumes new pregnancy cannot occur within six weeks of birth
- Live births among WPRA comprise child population
  - Pregnancy duration consistent with infant gestational age (and corresponding birthweight) from the joint low birthweight and short gestation (LBWSG) risk exposure from GBD
  - Pregnancy characteristics inform infant risk exposure



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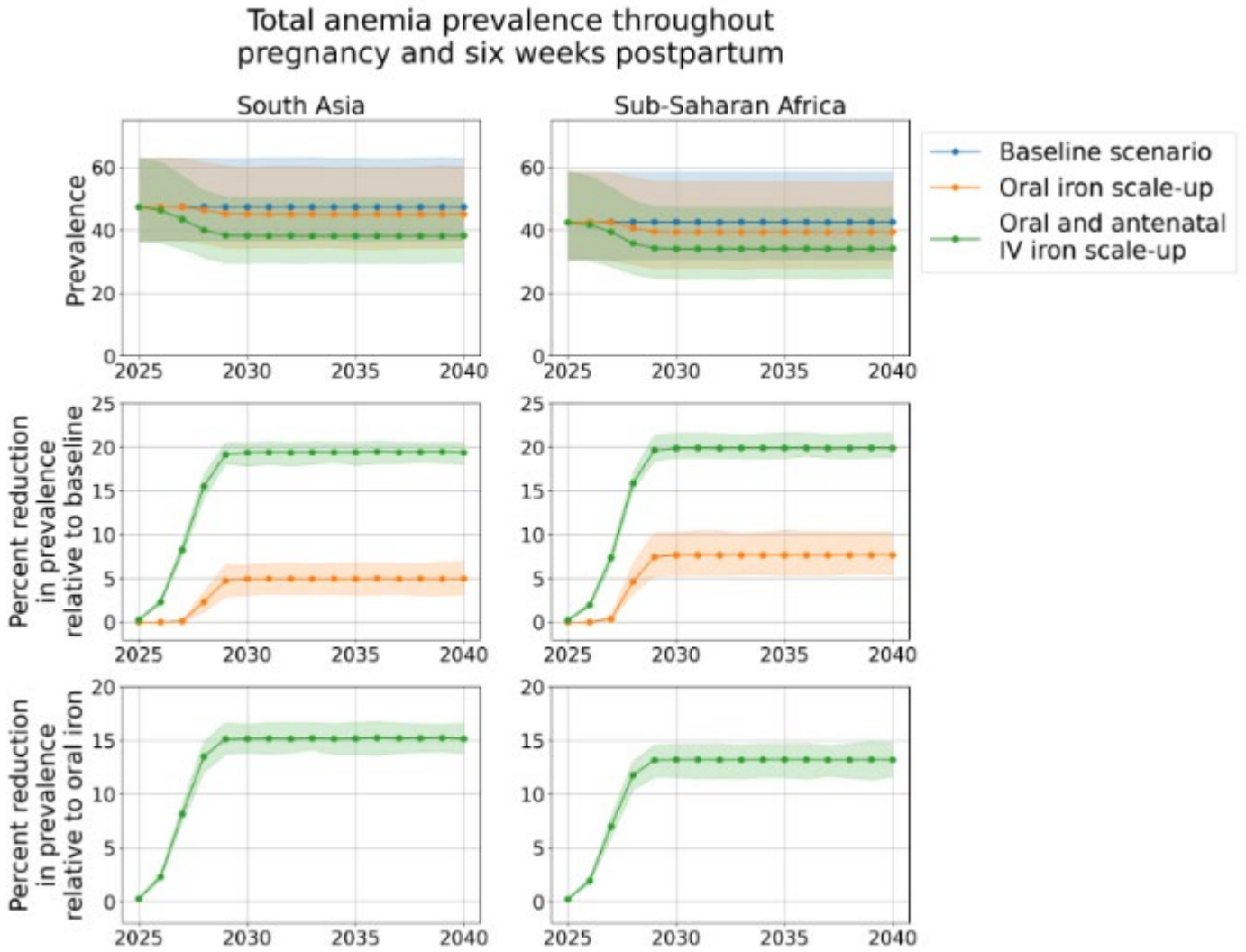
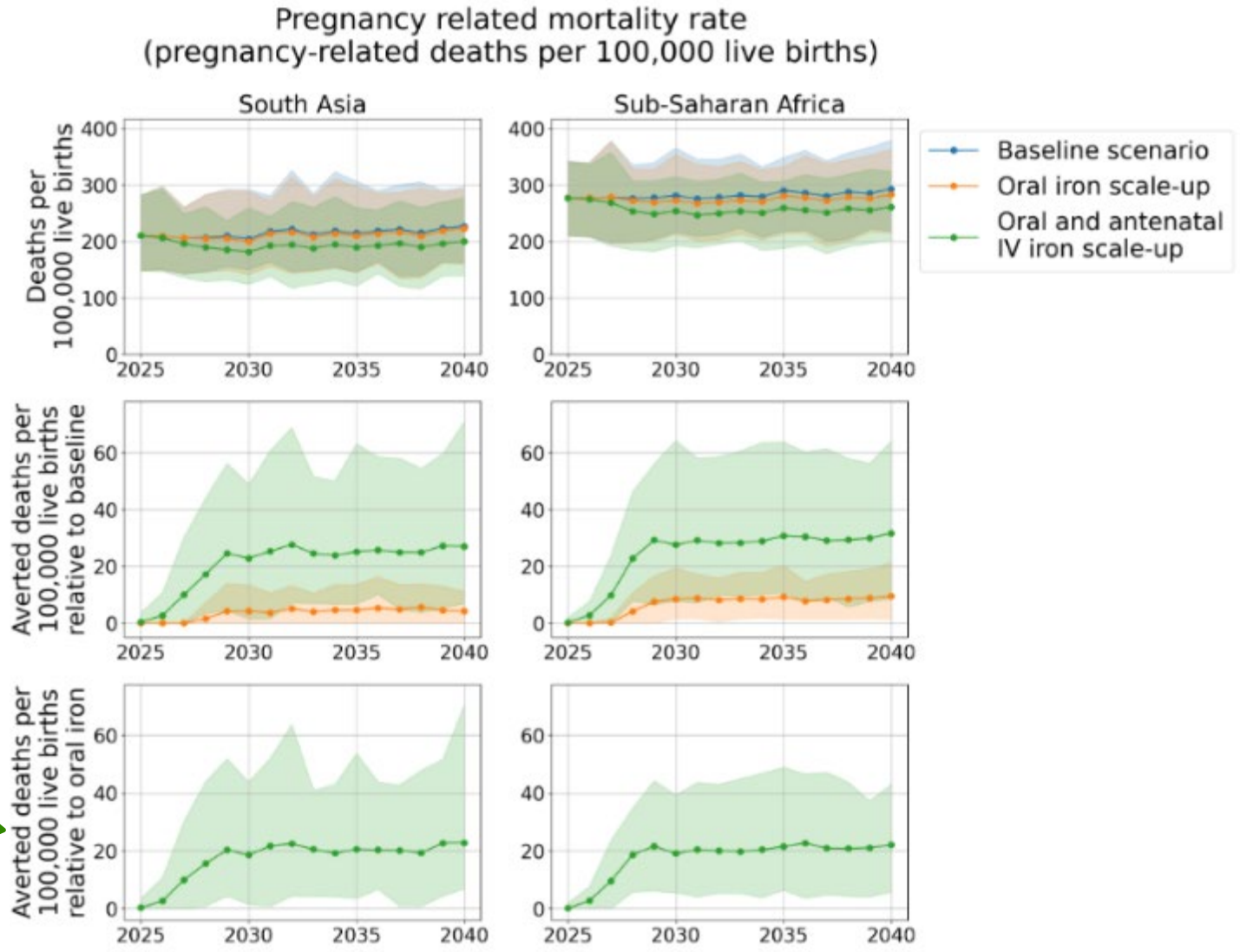
Antenatal IV iron interventions may reduce total anemia prevalence throughout pregnancy and six weeks postpartum by approximately 13 to 15 percent of what it would be with a scale-up of oral iron interventions

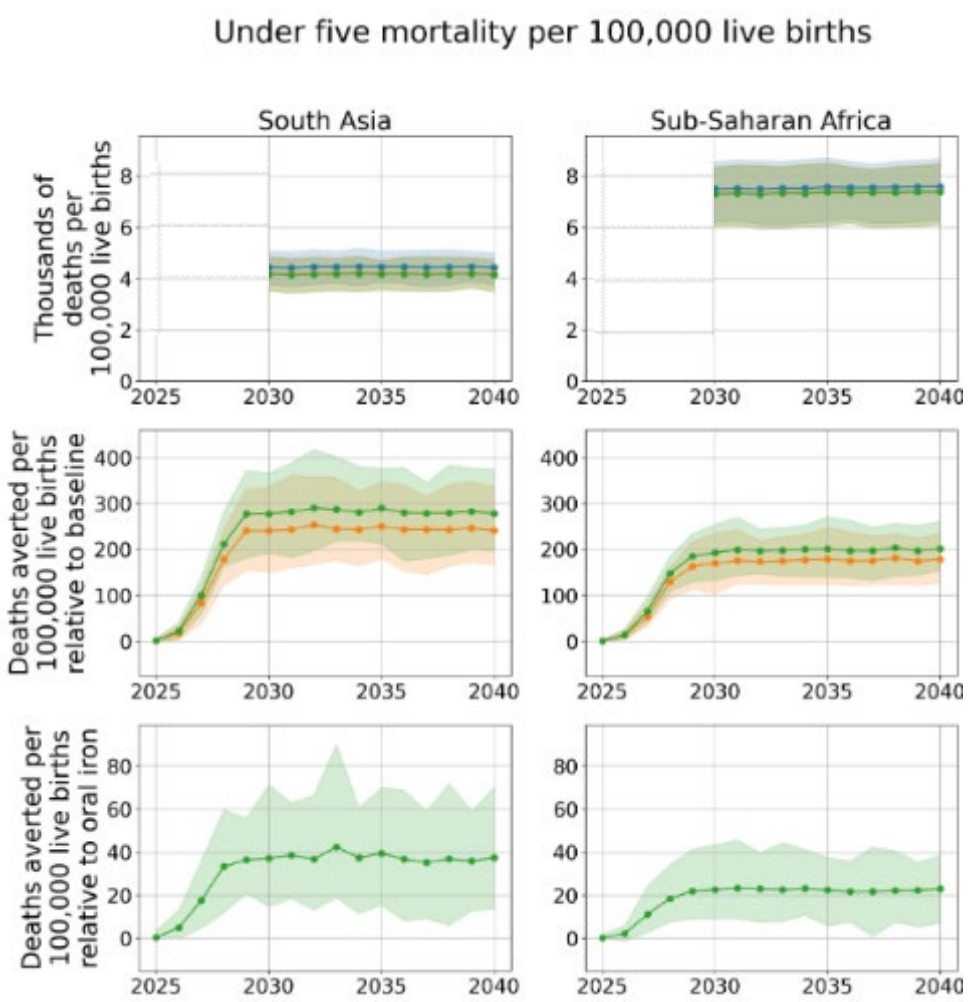


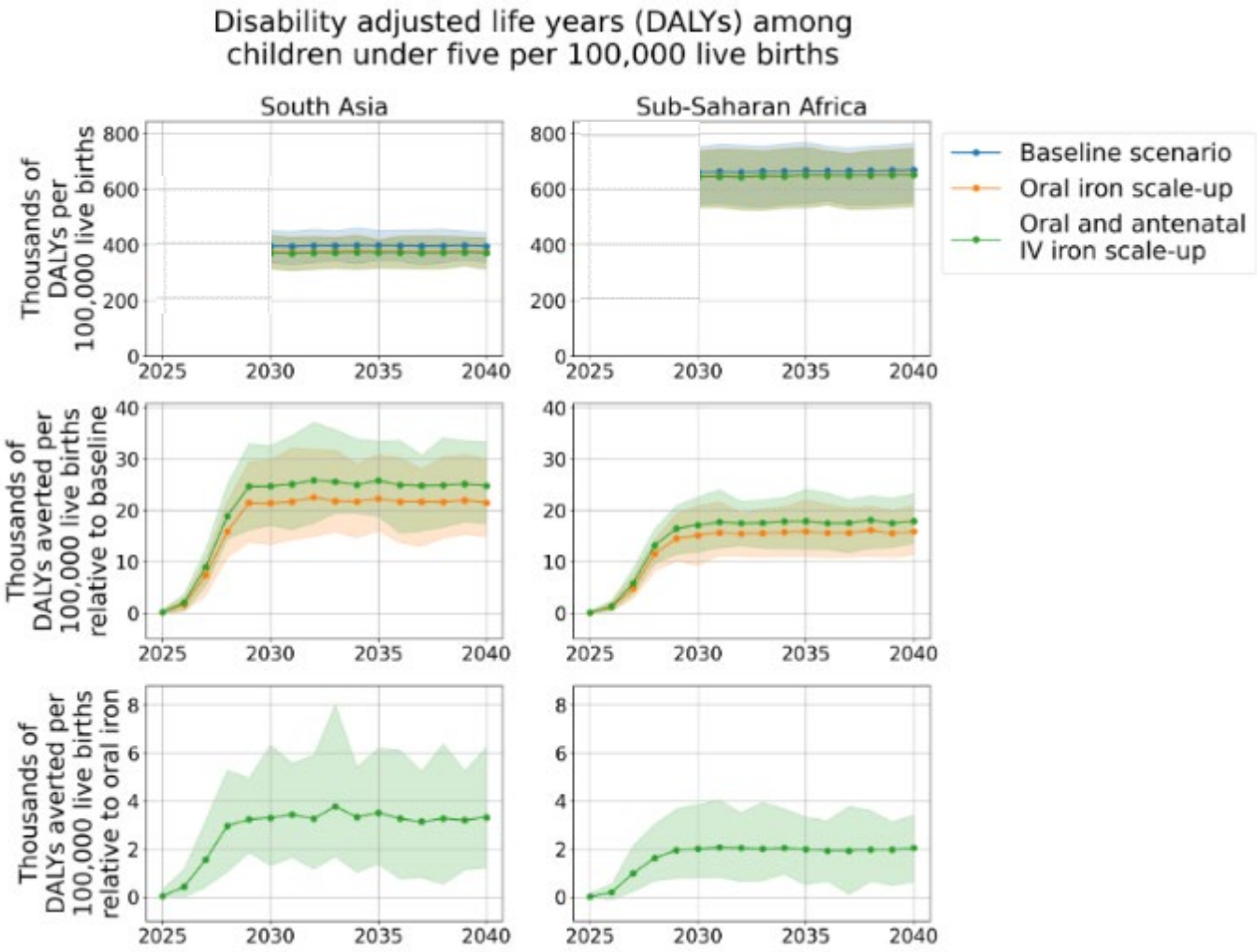
Antenatal IV iron scale-up in addition to a scale-up of oral iron may avert approximately 20 additional pregnancy related deaths per 100,000 live births



This is approximately 8.3k total deaths averted in South Asia and 11.3k in Sub-Sharan Africa

Intervention impacts on morbidity and mortality among children under five (neonates)

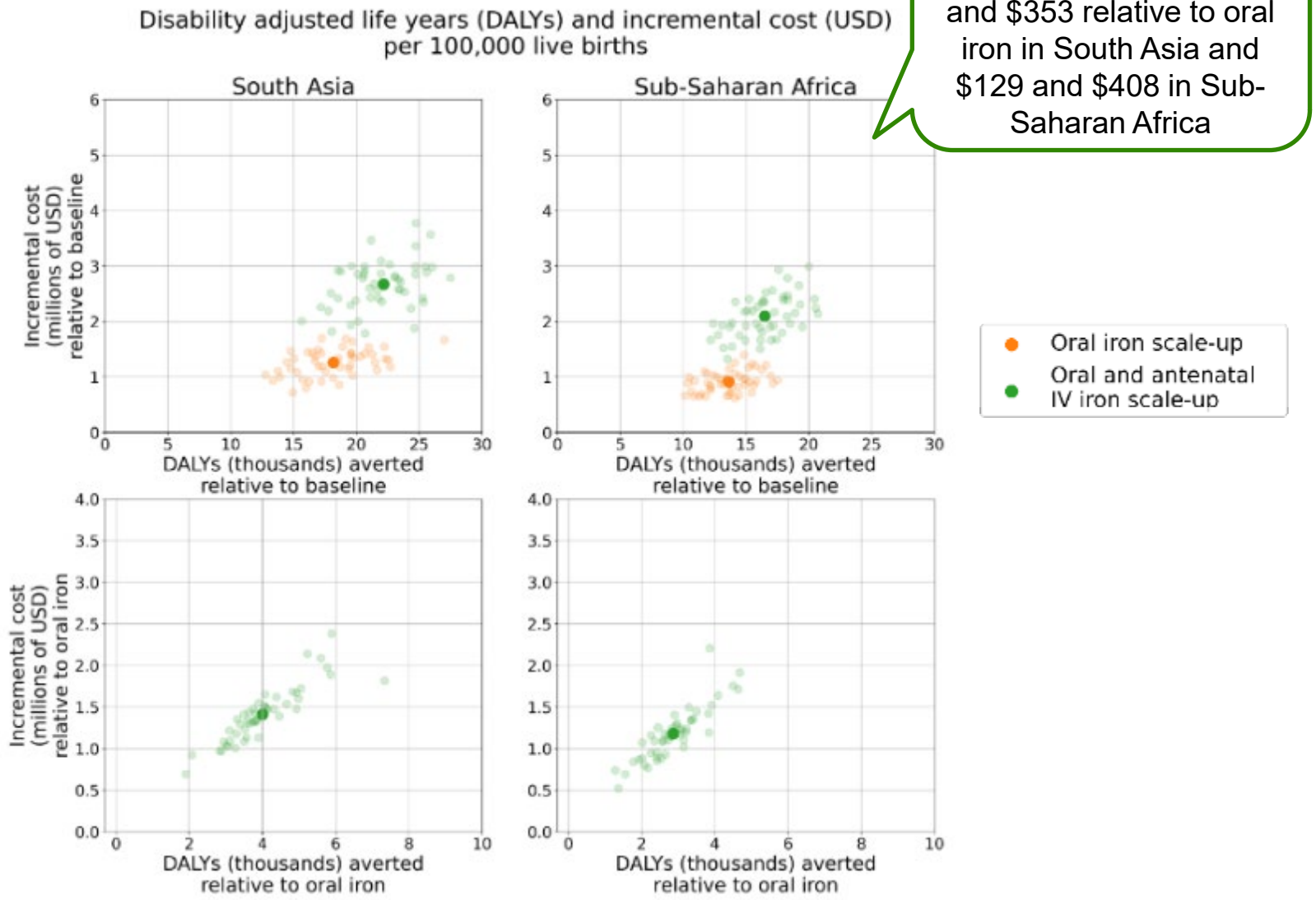




This is approximately 85k total deaths averted in South Asia and 71k in Sub-Sharan Africa

Estimates of incremental costs were calculated based on product cost estimates

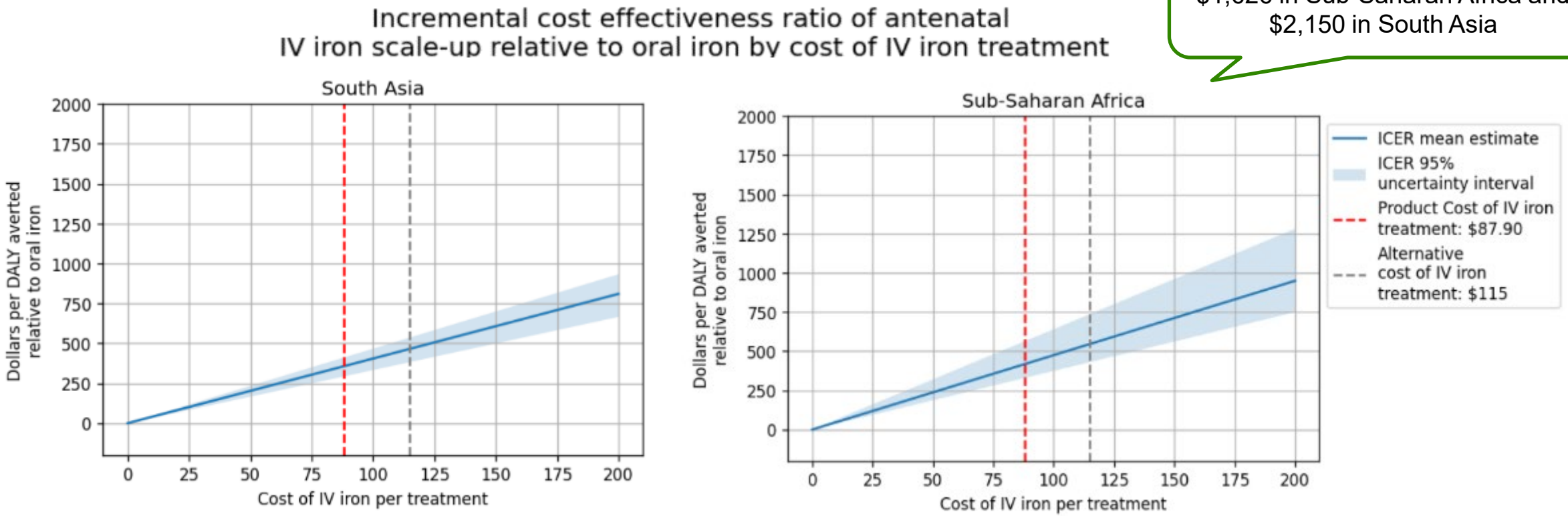
Scenario Added	Intervention	Product Cost
Baseline Only	IFA	$0.91
Oral Iron Scale-Up	MMS	$2.98
	BEP	$60
Oral Iron Scale-Up and Antenatal IV Iron	Antenatal IV iron	$87.90



The incremental cost is $120 relative to baseline and $353 relative to oral iron in South Asia and $129 and $408 in Sub-Saharan Africa

Sensitivity analysis: Antenatal IV iron incremental cost effectiveness ratio relative to oral iron is sensitive to the cost of IV iron treatment

The GDP per capita in 2021 was $1,626 in Sub-Saharan Africa and $2,150 in South Asia



Sensitivity analysis cost estimate of 117.90 USD from:

- $87.90 product cost from Jose et al. (2019) FCM trial in India
- $30 IV administration cost from Mosegui et al. (2019) CEA of oral versus IV dehydration treatment in Brazil

Future directions for results

- Our model is also able to include postpartum intravenous iron, which when tested showed limited impact over antenatal only
- In addition to modeled effects on child outcomes, we hope to include the impact of orphanhood and breastfeeding/chest feeding, further allowing pregnancy related outcomes to impact children
- We would like to further improve our costing model to include additional detail such as: supply chain costs, administration costs and transition or changeover costs

Acknowledgements

We would like to thank everyone who made this work possible:

- Past and present members of the Simulation Science Team including Abraham Flaxman, Ali Bowman, Alix Pletcher, Rajan Mudambi, Matt Kappel, Jim Albright, Hussain Jafari, James Collins, Nathaniel Blair-Stahn, Paulina Lindstedt, Caroline Kinuthia, Nicole Young, and Kjell Swedin

- All GBD modelers at IHME for their work on the GBD study that makes our work possible with the use of their data. Most especially the neonatal and child health and maternal health teams.

- Our partners at the Bill and Melinda Gates Foundation for their support including Laura Lamberti, Kate Fay, and Sun-Eun Lee

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Thank you!

Questions?

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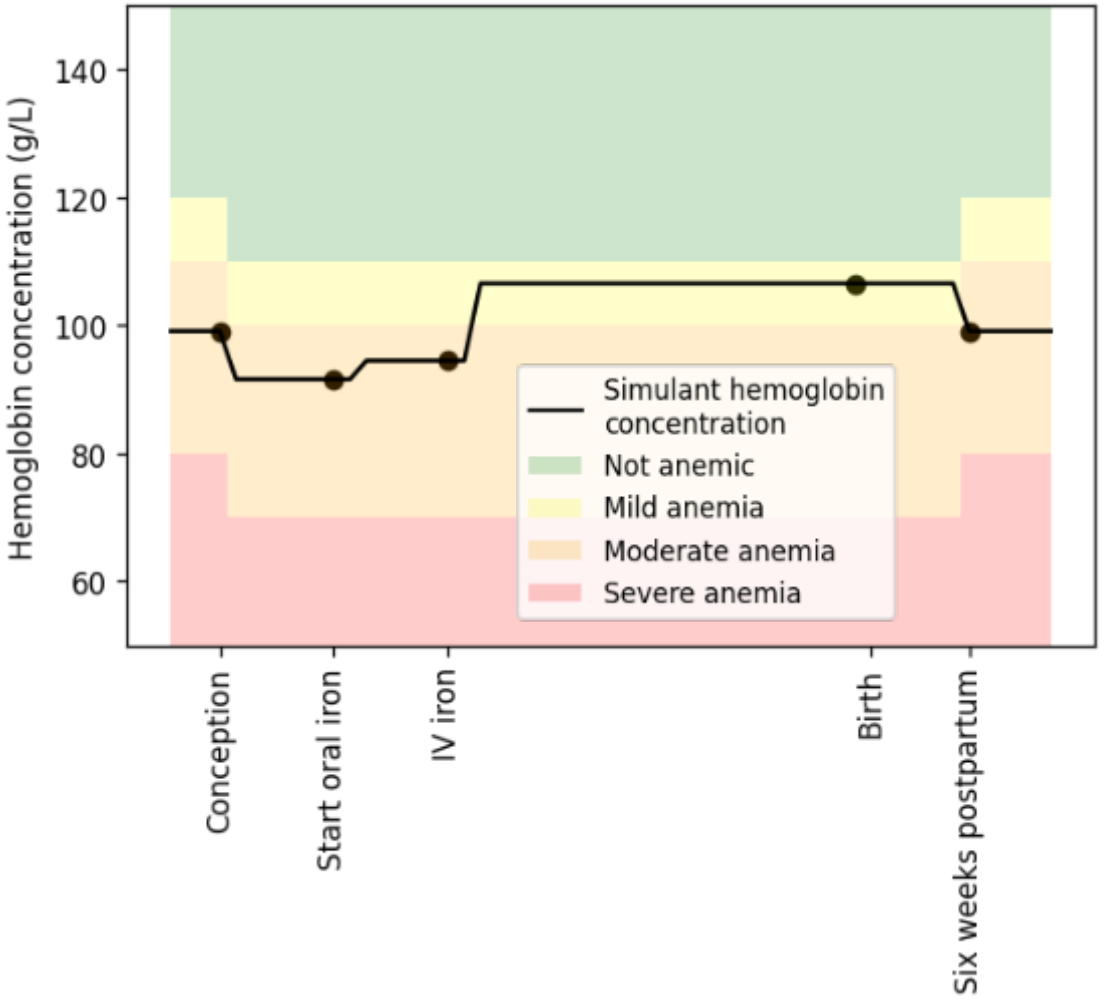
- **Appendix**

Simulant hemoglobin trajectories throughout pregnancy

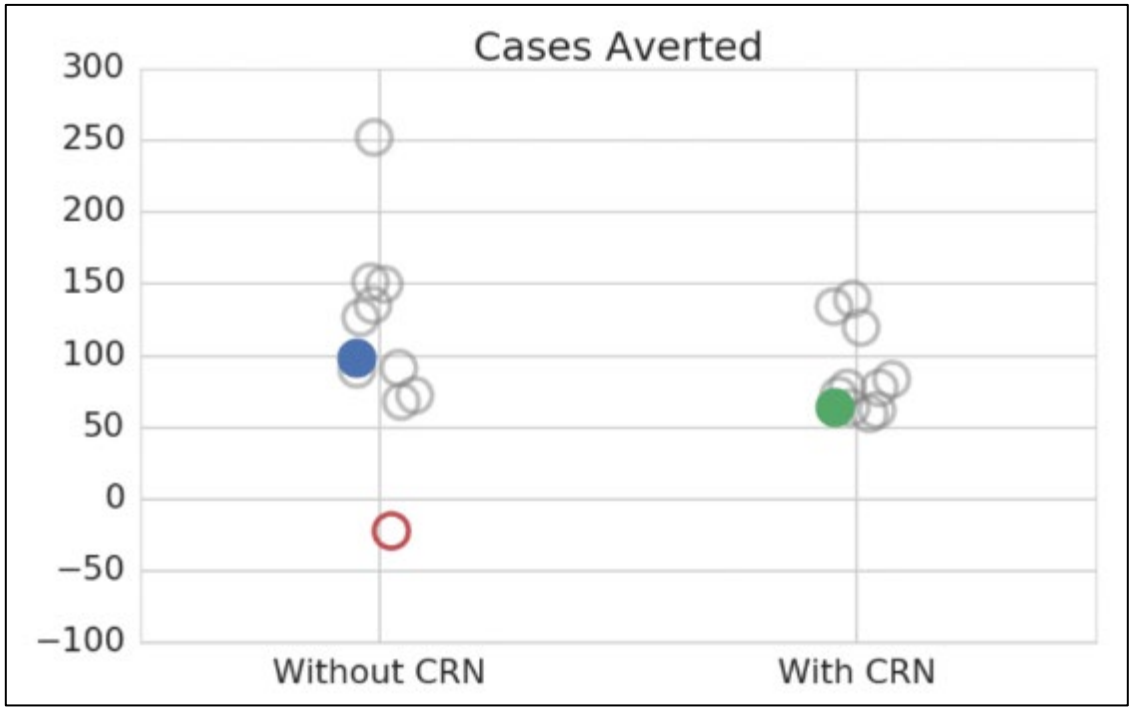
Population	Mild anemia hemoglobin threshold (g/L)	Moderate anemia hemoglobin threshold (g/L)	Severe anemia hemoglobin threshold (g/L)
Women 15 – 49, not pregnant	120 – 110	110 – 80	<80
Women 15 – 49, pregnant	110 – 100	100 - 70	<70

Anemia severity	Disability Weight
Mild	0.004
Moderate	0.052
Severe	0.149



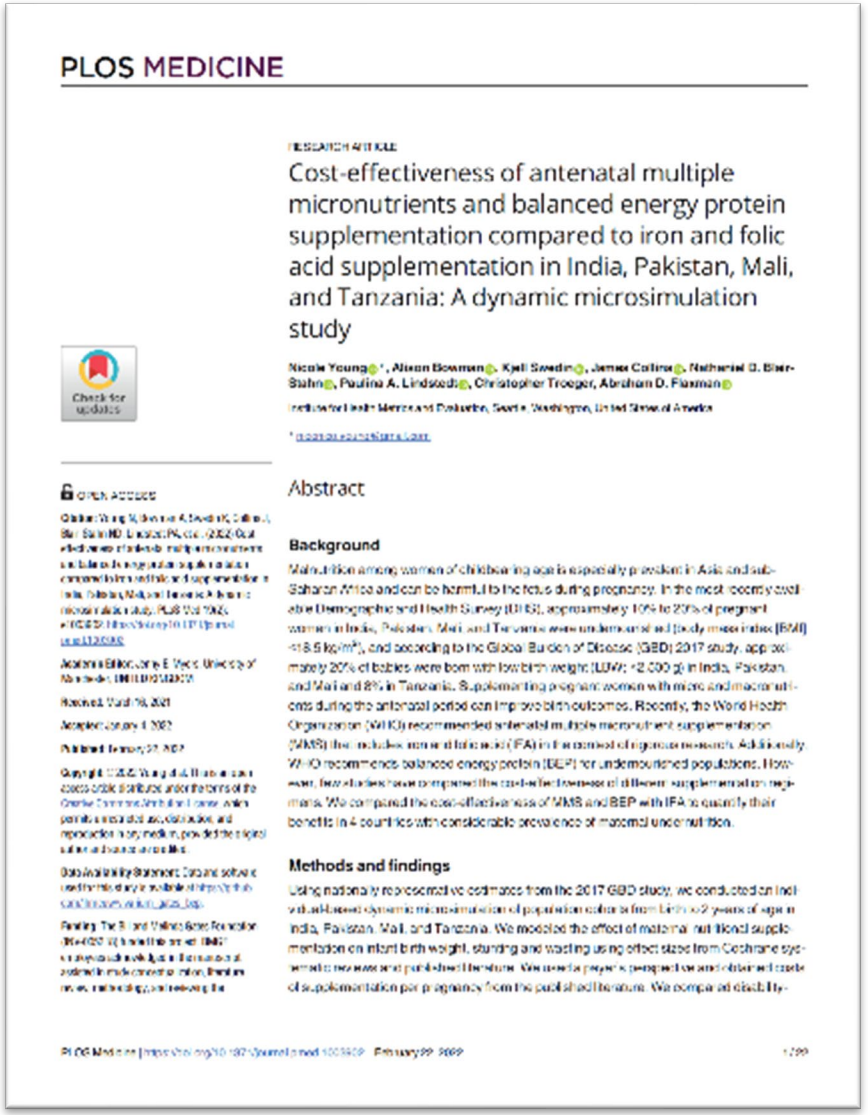
Common random numbers

- We utilize common random numbers to avoid over-estimating the impact of uncertainty
- This creates a population in each baseline and alternative scenario with the same:
  - Heterogeneous population
  - Starting parameter values
  - Random chance of experiencing events
- Uncertainty is still included in the simulation, but is not incorrectly increased by being included between scenarios



Examples of previous projects

- Dynamic transition model of child wasting (in progress)
  - Used to investigate moderate and severe acute malnutrition case loads under various combinations of coverage scale-ups for:
    - Community management of acute malnutrition intervention for severe, moderate, or both
    - Small quantity lipid-based nutrient supplementation, targeted or universal
- Cost-effectiveness of antenatal multiple micronutrients (MMS) and balanced energy protein (BEP) supplementation compared to iron and folic acid (IFA) supplementation[1]
  - Assessed impact and costs of various scale-up strategies, including targeted and universal BEP supplementation, among children under two years of age
  - Found that MMS + BEP targeted to those with BMI < 18.5 is similarly cost effective to universal MMS



PLOS MEDICINE

RESEARCH ARTICLE

Cost-effectiveness of antenatal multiple micronutrients and balanced energy protein supplementation compared to iron and folic acid supplementation in India, Pakistan, Mali, and Tanzania: A dynamic microsimulation study

Abstract

Background

Methods and findings

Intravenous Iron Microsimulation Research Question

Simulation research question	
Key outcomes:	Impact on disability adjusted life years (DALYs)
Intervention:	Scaled-up coverage of antenatal and postpartum IV iron interventions
Comparator:	Scaled-up coverage MMS and targeted BEP from baseline IFA
Population:	Women aged 15-49 and children under five years of age
Locations:	South Asia and Sub-Saharan Africa (India, Nigeria, and Ethiopia to come)
Timeframe:	2025 to 2040
Key assumptions:	• BMGF “optimistic target product profiles” for IV iron interventions • Reach 100% coverage of eligible population at point of care by 2029

Intervention impact on child growth failure

- Lack of literature evidence on intervention impact on child wasting and stunting
  - Lack of follow-up beyond birth outcomes
  - Small effects require large sample sizes
- Literature evidence on *causal* impact of birthweight improvement on child wasting and stunting exposure
  - McGovern 2018: study of twins and sibling pairs using DHS data
    - The marginal effect of a 200g increase in birthweight is associated with a 1.1-1.2 percentage point decrease in the probability of wasting and a 2.0 (SD: 0.6) to 2.3 (SD: 0.5) percentage point decrease in the probability of stunting among children under five
- Interventions impact on CGF entirely mediated through effect on birthweight

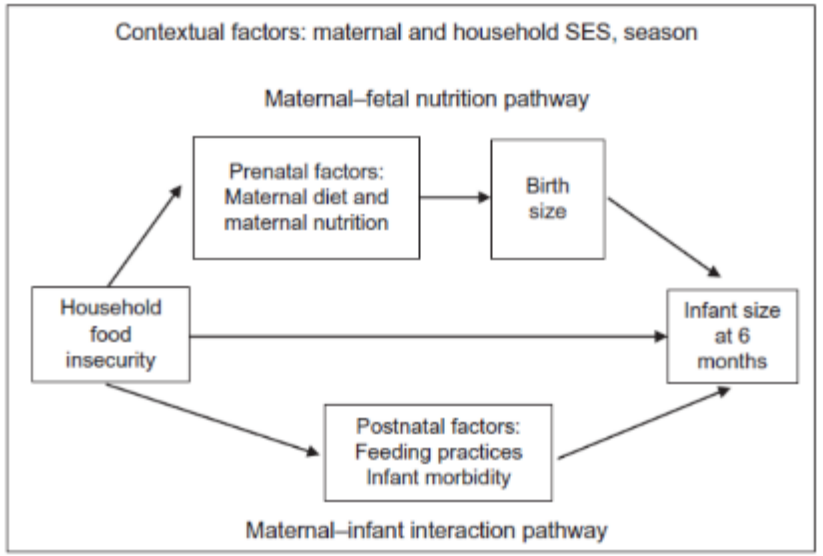


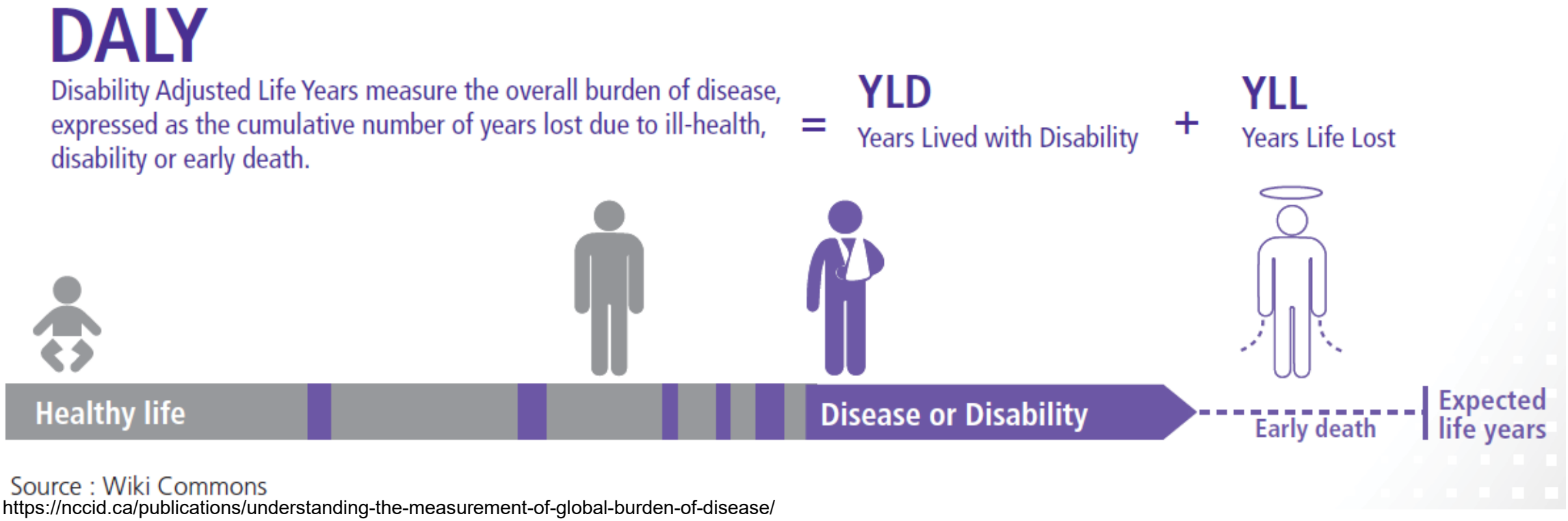
Figure from Na et al. 2020

McGovern M. E. (2019). How much does birth weight matter for child health in developing countries? Estimates from siblings and twins. *Health economics*, *28*(1), 3–22.
Na, M., Shamim, A. A., Mehra, S., Labrique, A., Ali, H., Wu, L. S., Shaikh, S., Klemm, R., Christian, P., & West, K. P. (2020). Maternal nutritional status mediates the linkage between household food insecurity and mid-infancy size in rural Bangladesh. *The British journal of nutrition*, *123*(12), 1415–1425.

Impact of CGF pathway varies by location and age group

- Pathway through CGF represents a greater portion of DALYs averted in Sub-Saharan Africa than South Asia
  - Expected due to differences in regional epidemiology
    - On average, lower birthweight in South Asia than Sub-Saharan Africa
    - On average, greater CGF exposure and affected cause burden in Sub-Saharan Africa than South Asia
- Pathway through CGF has greater impact among post-neonates (1 month to 1 year) than children 1 to 4 years of age
  - Expected due to CGF-associated burden in the younger age group
  - Note that we did not model age-specific associations between birthweight and CGF exposures, which would be expected to exaggerate this finding further

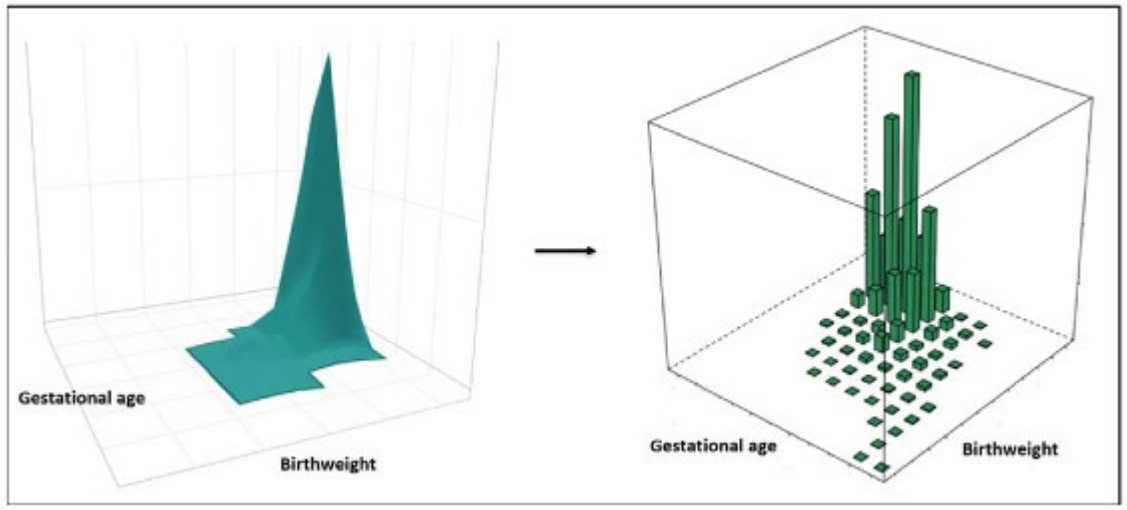
Disability adjusted life years, reviewed



Source : Wiki Commons
https://nccid.ca/publications/understanding-the-measurement-of-global-burden-of-disease/

Infant birthweight and gestational age

- Each simulated live birth assigned point values for birthweight (grams) and gestational age at birth (weeks)
  - Informed from joint categorical distribution estimated in GBD
- Birthweight exposure may be additionally modified by maternal characteristics and intervention coverage
  - Assume no associated changes in gestational age at birth
- Applied an interpolated smoothed risk surface across categorical relative risk values from GBD so that birthweight increases within existing categories resulted in decreased risk as well as birthweight increases that result in crossing category boundaries



Woman first trial for correlation

- Multi-country randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception, including sites in rural locations of the Democratic Republic of the Congo (DRC), Guatemala, India, and Pakistan
  - BMI exposure measurement preference was pre-pregnancy closest to conception or, if unavailable, first measurement in the first trimester
  - Hemoglobin exposure measurement preference was 2nd trimester, 1st trimester, 3rd trimester
- Unadjusted relative risk of BMI < 18.5 among those with hemoglobin < 10 g/dL relative to those with hemoglobin of 10 or more g/dL equal to 2.07 (95% CI: 1.79, 2.39)

Category	Birth weight mean difference relative to BMI ≥ 18.5 and hemoglobin ≥ 10 g/dL, in grams (95% CI)
BMI ≥ 18.5, hemoglobin < 10 g/dL	-94 (-142, -46)
BMI < 18.5, hemoglobin ≥ 10 g/dL	-182 (-239, -125)
BMI < 18.5, hemoglobin < 10 g/dL	-275 (-336, -213)

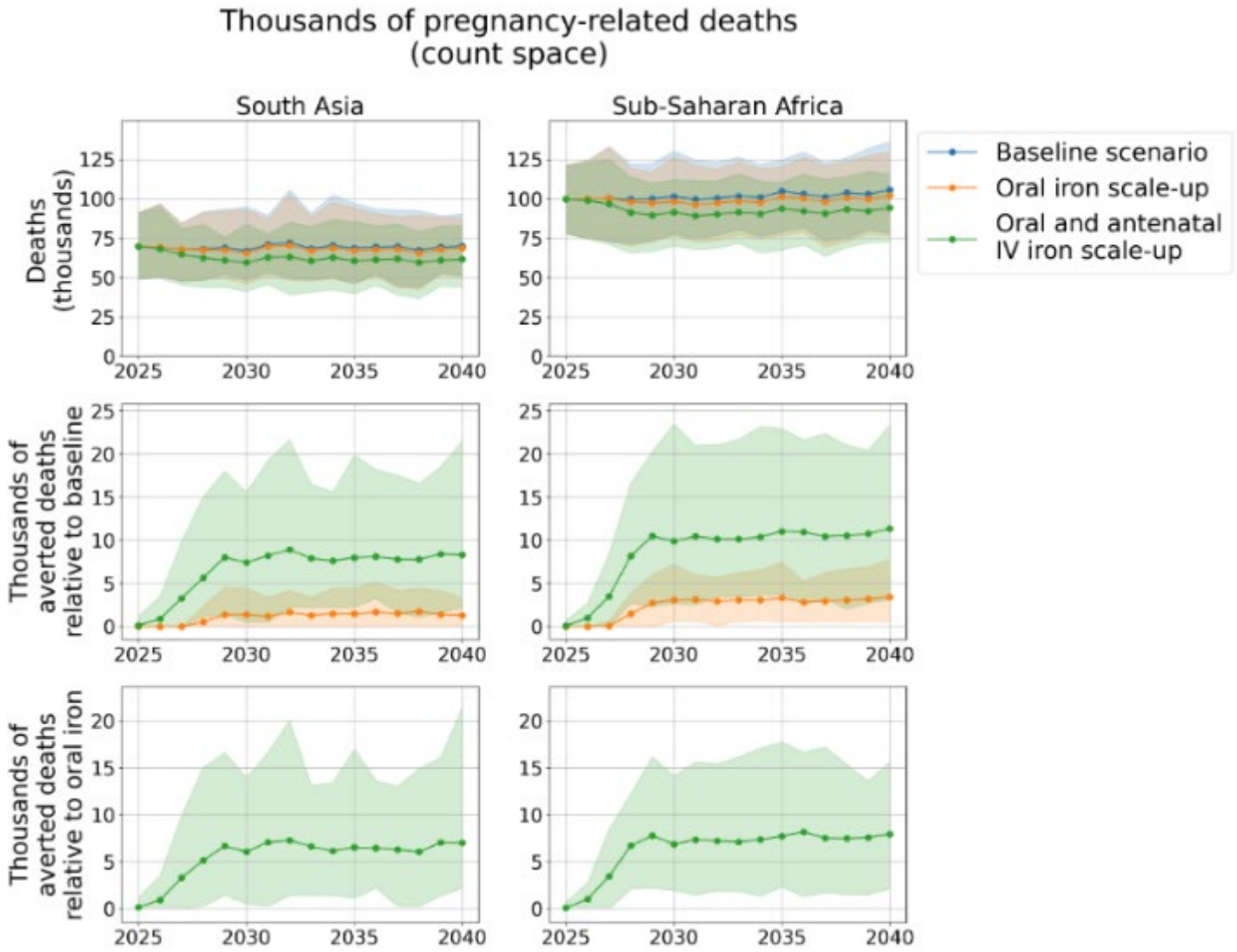
Hambidge KM, Westcott JE, Garcés A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshefu A, Lokangaka A, Derman RJ, Goldenberg RL, Bose CL, Bauserman M, Koso-Thomas M, Thorsten VR, Sridhar A, Stolka K, Das A, McClure EM, Krebs NF; Women First Preconception Trial Study Group. A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial. Am J Clin Nutr. 2019 Feb 1;109(2):457-469. doi: 10.1093/ajcn/nqy228. PMID: 30721941; PMCID: PMC6367966.

Hemorrhage and hemoglobin

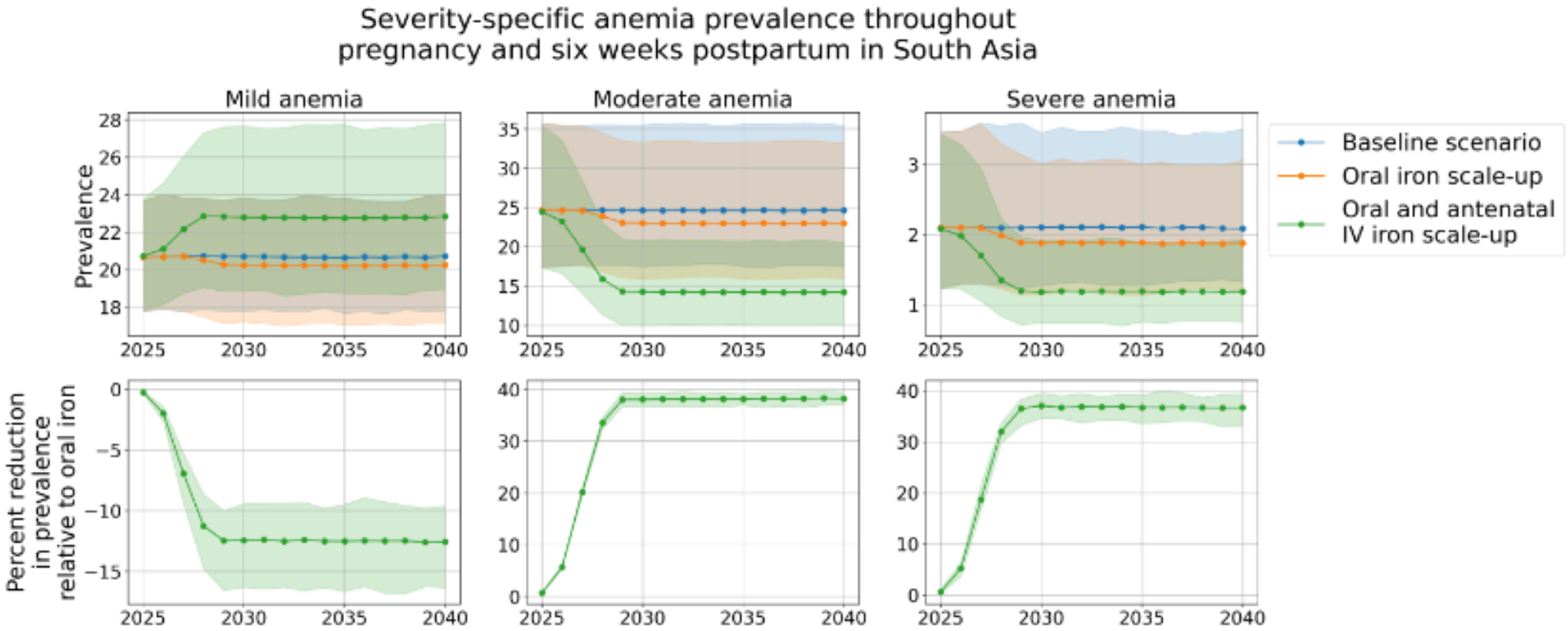
- Postpartum hemorrhage modeled as an incident cause at birth with no YLDs or YLLs
  - YLDs and YLLs included as a sub-cause in the maternal disorders parent cause component
  - Incidence informed from GBD sub-cause
- Allowed us to model:
  - Effect of hemoglobin at birth on postpartum hemorrhage incidence
    - Omotayo et al. (2021) systematic review: severe anemia OR: 3.54 (1.2, 10.4)
  - Effect of hemorrhage on hemoglobin
    - Hemorrhage severity fraction informed from GBD sequelae
    - Assumed 750 mL and 1,250 mL blood loss for moderate (500-1,000 mL) and severe (>1,000 mL) hemorrhage, respectively
    - Assumed blood volume at birth equal to 7.5 liters, under the assumptions of a 50% increase in plasma blood volume in the late third trimester[6,7]
    - Assumed proportional reduction in hemoglobin that persists for six weeks postpartum without intervention

Omotayo, M. O., Abioye, A. I., Kuyebi, M., & Eke, A. C. (2021). Prenatal anemia and postpartum hemorrhage risk: A systematic revie and meta-analysis. Journal of Obstetrics and Gynaecology Research, 47(8), 2565–2576. https://doi.org/10.1111/jog.14834

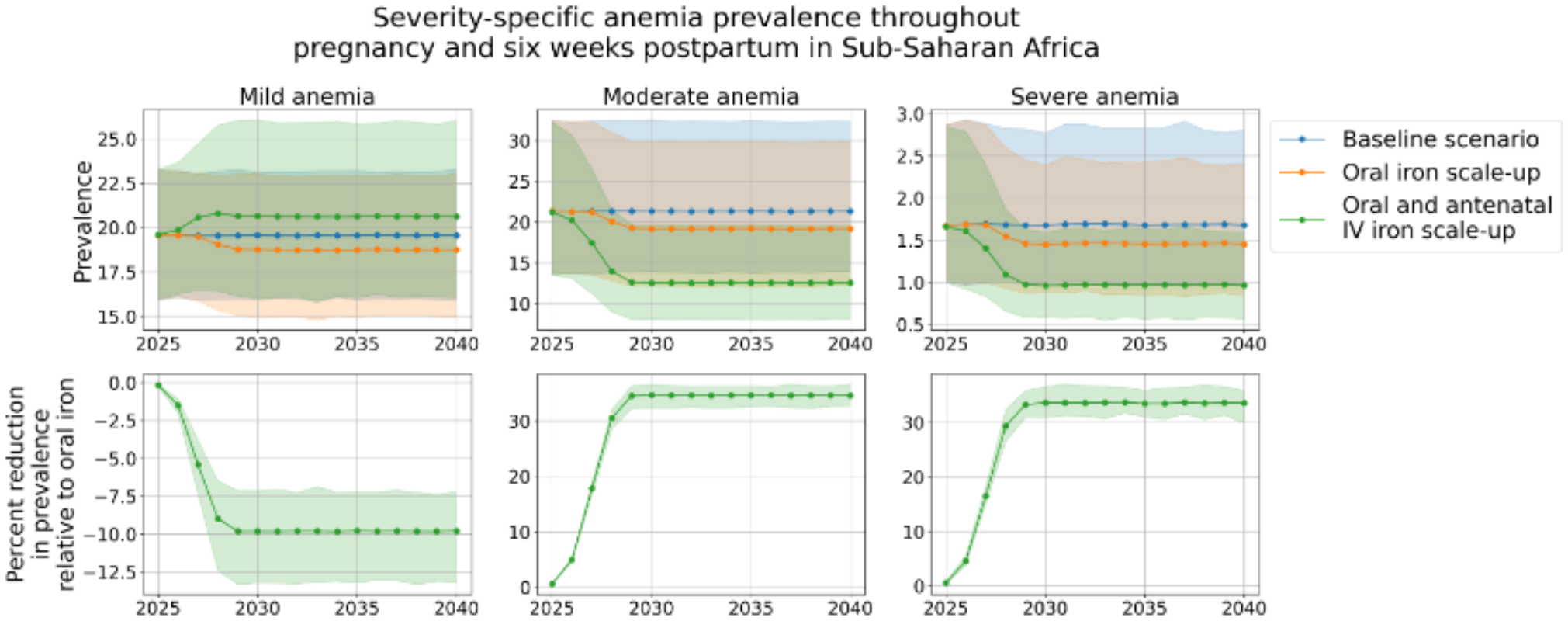
Pregnancy related deaths averted *(count space)*



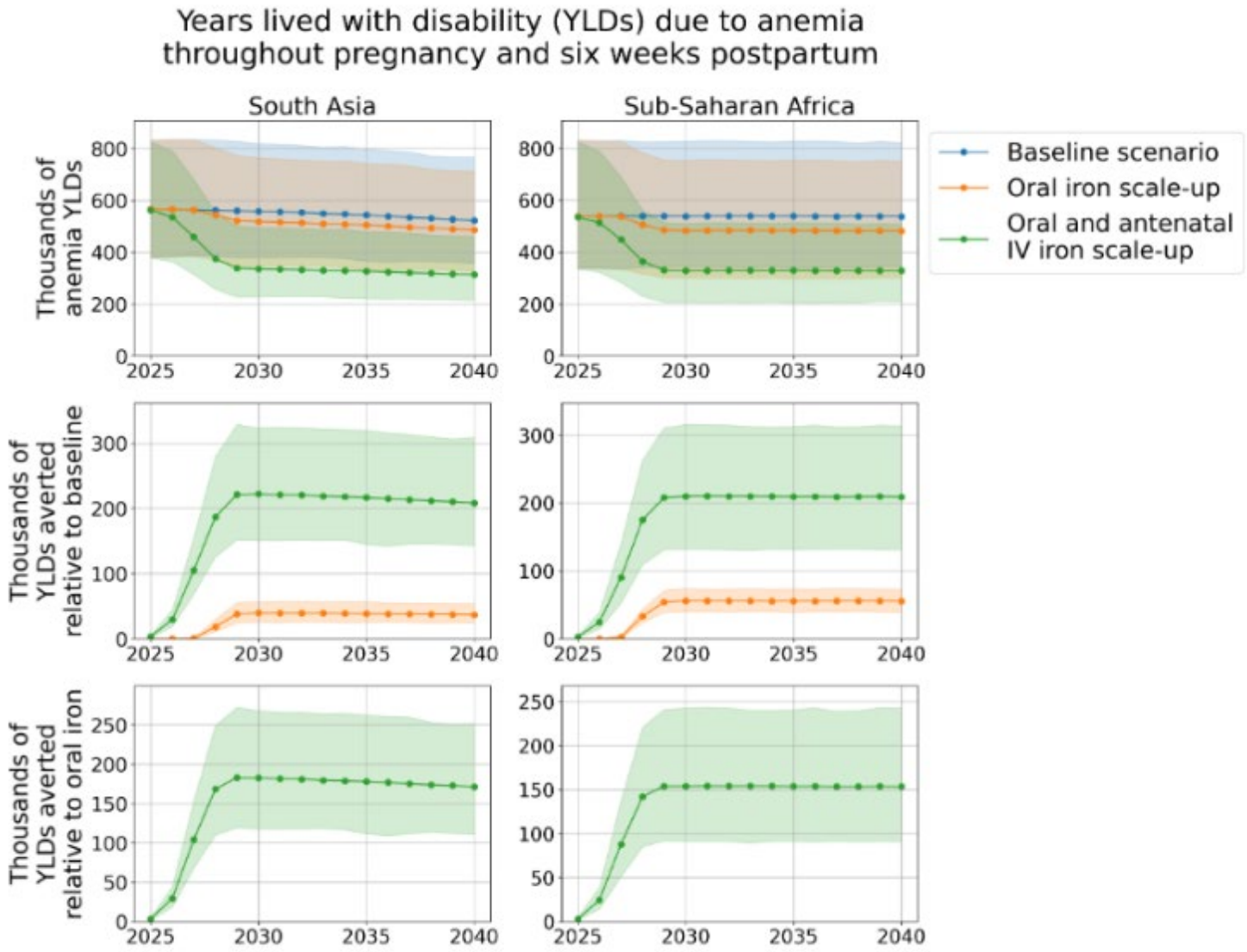
Severity specific anemia prevalence in South Asia



Severity specific anemia prevalence in Sub-Saharan Africa

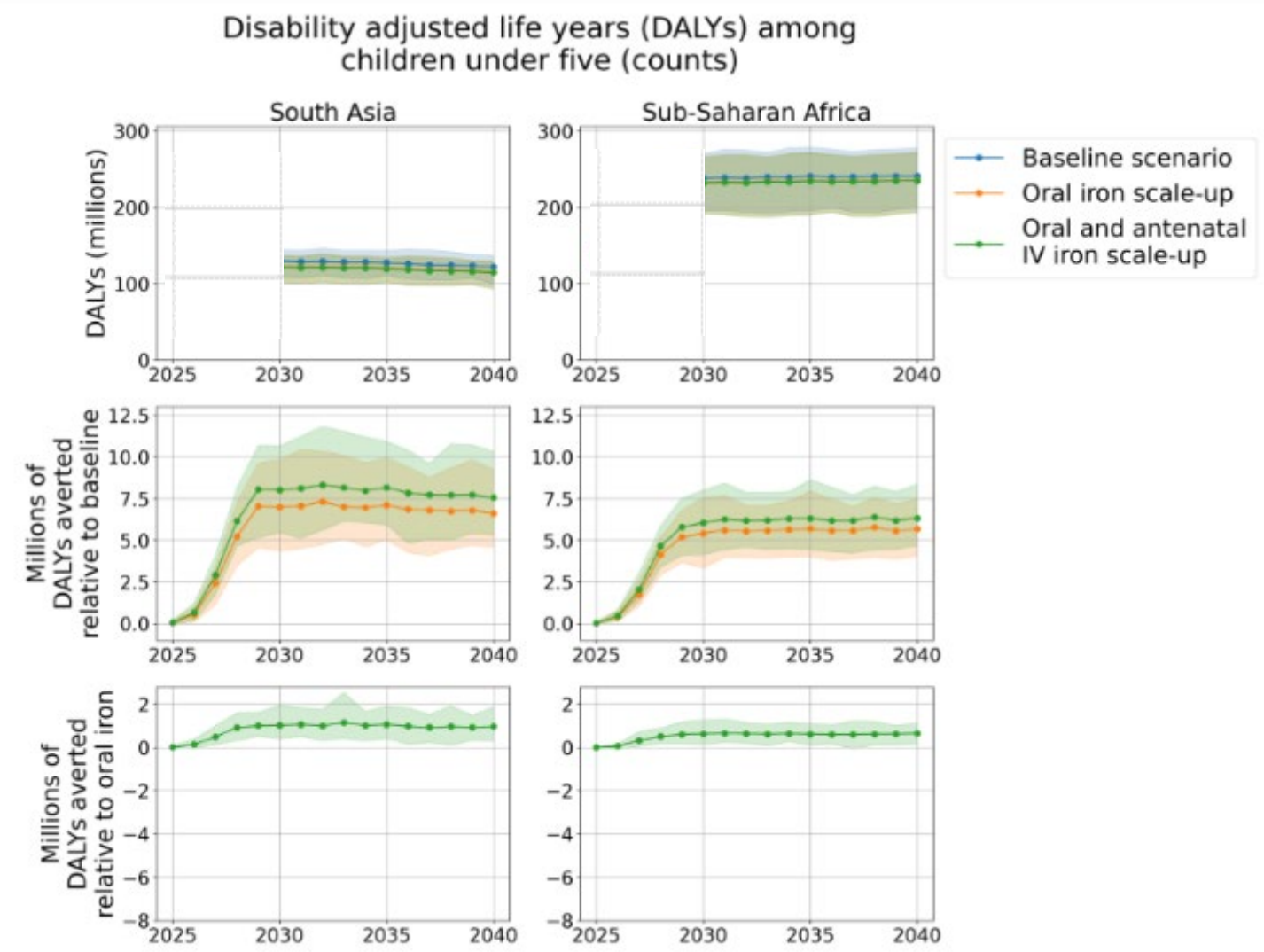


Anemia YLDs Averted *(count space)*

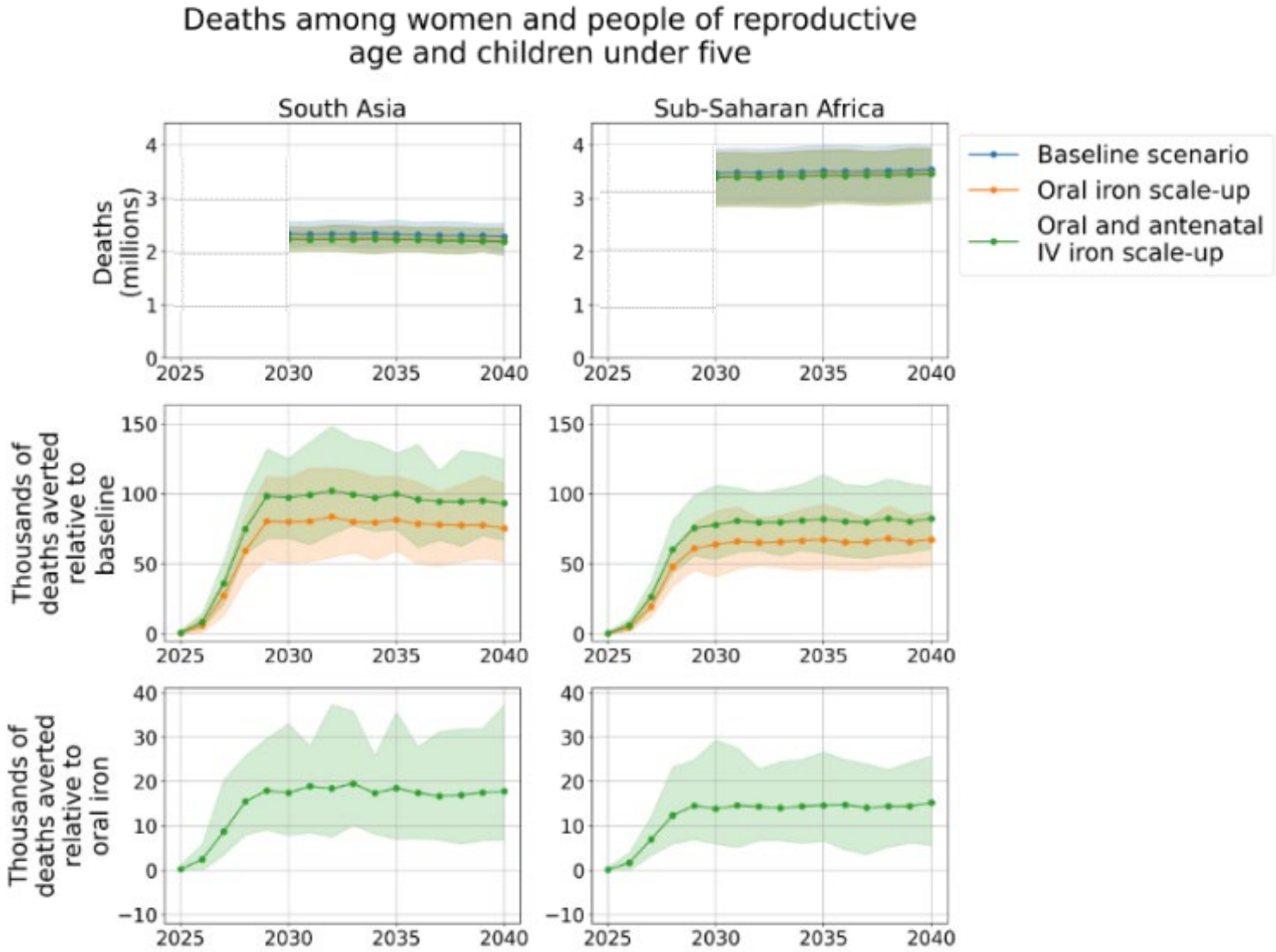


Deaths among children averted *(count space)*

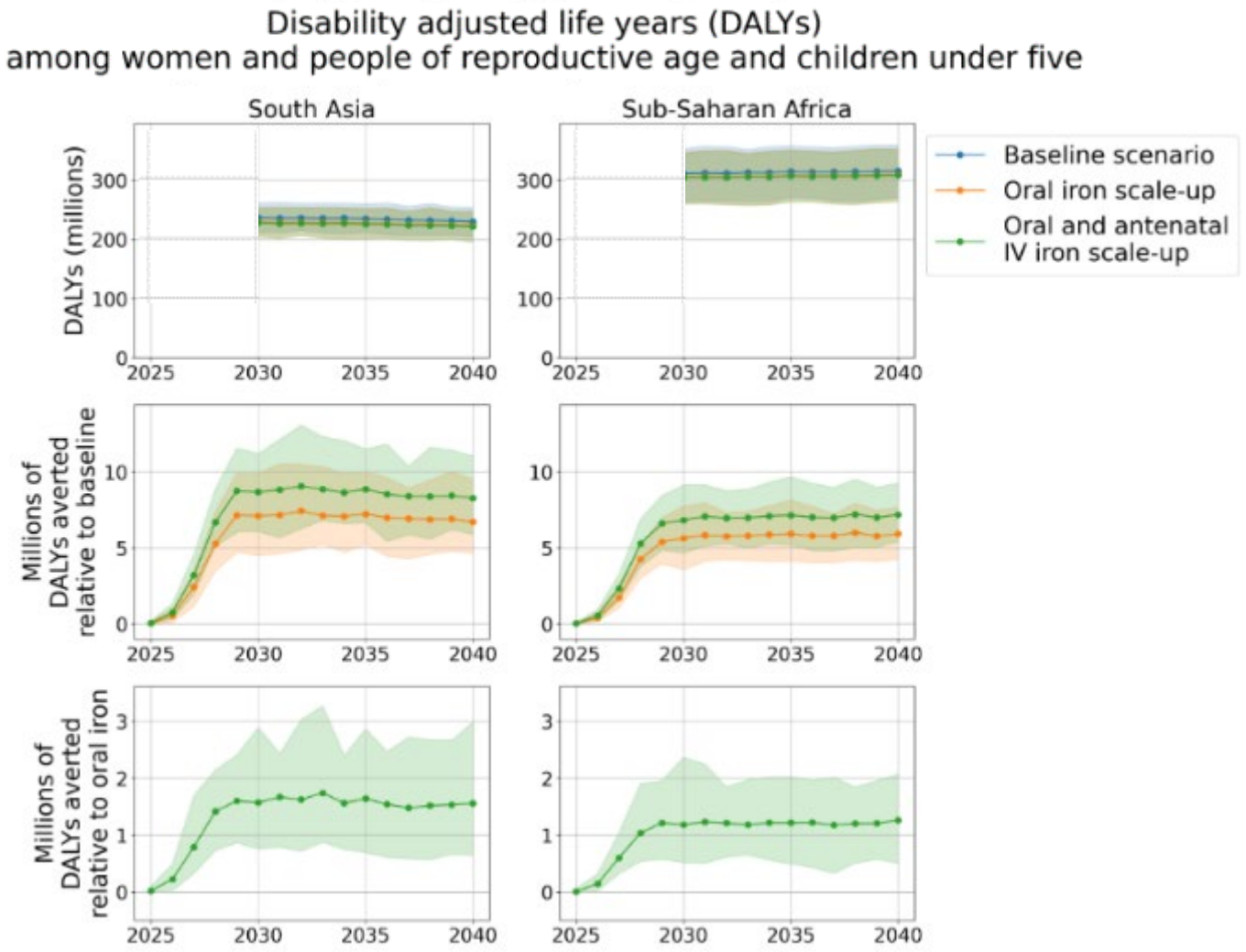
DALYs among children averted *(count space)*



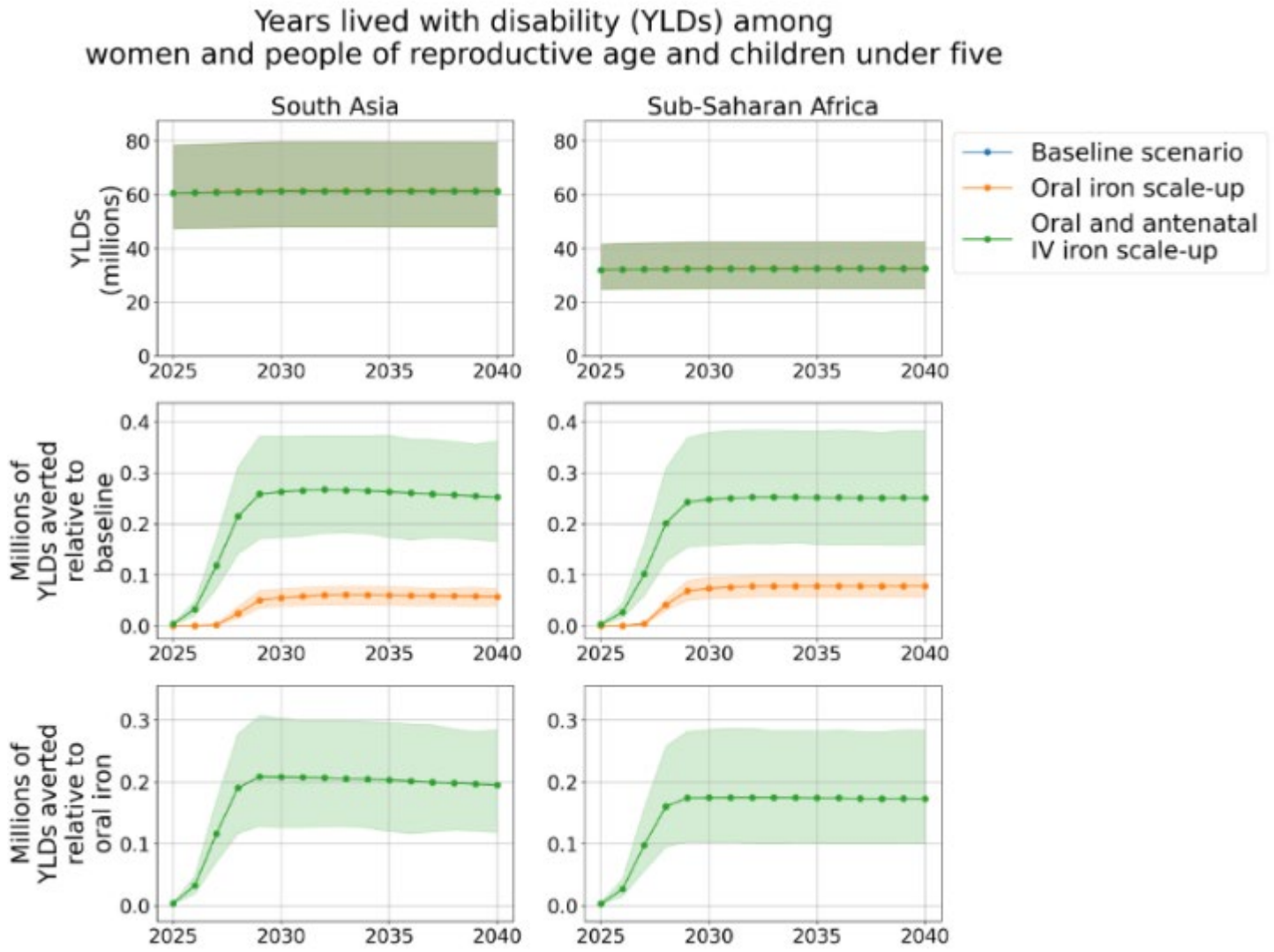
Pregnancy related and child deaths averted *(count space)*



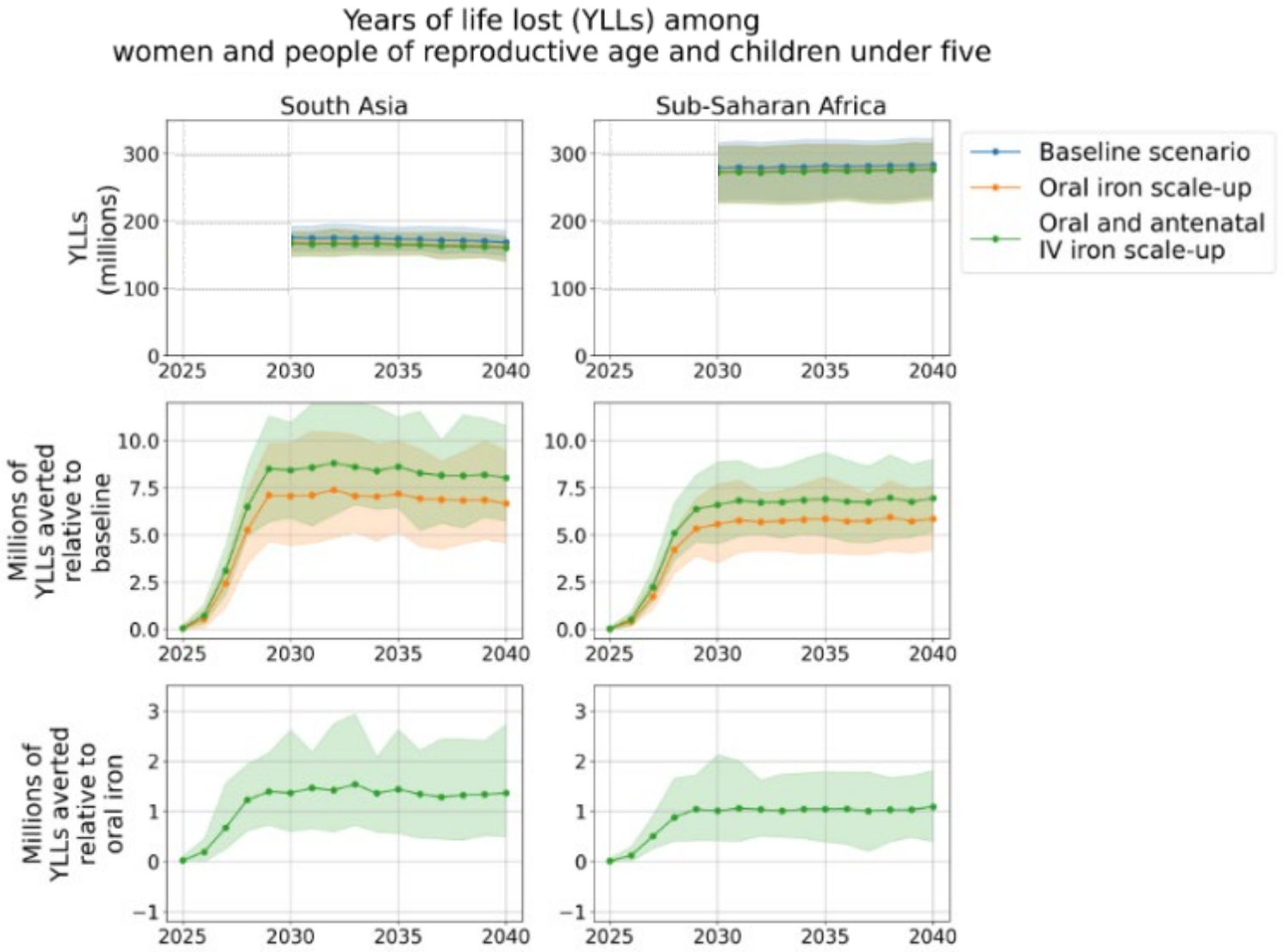
DALYs averted for women or reproductive age and children under 5 *(count space)*



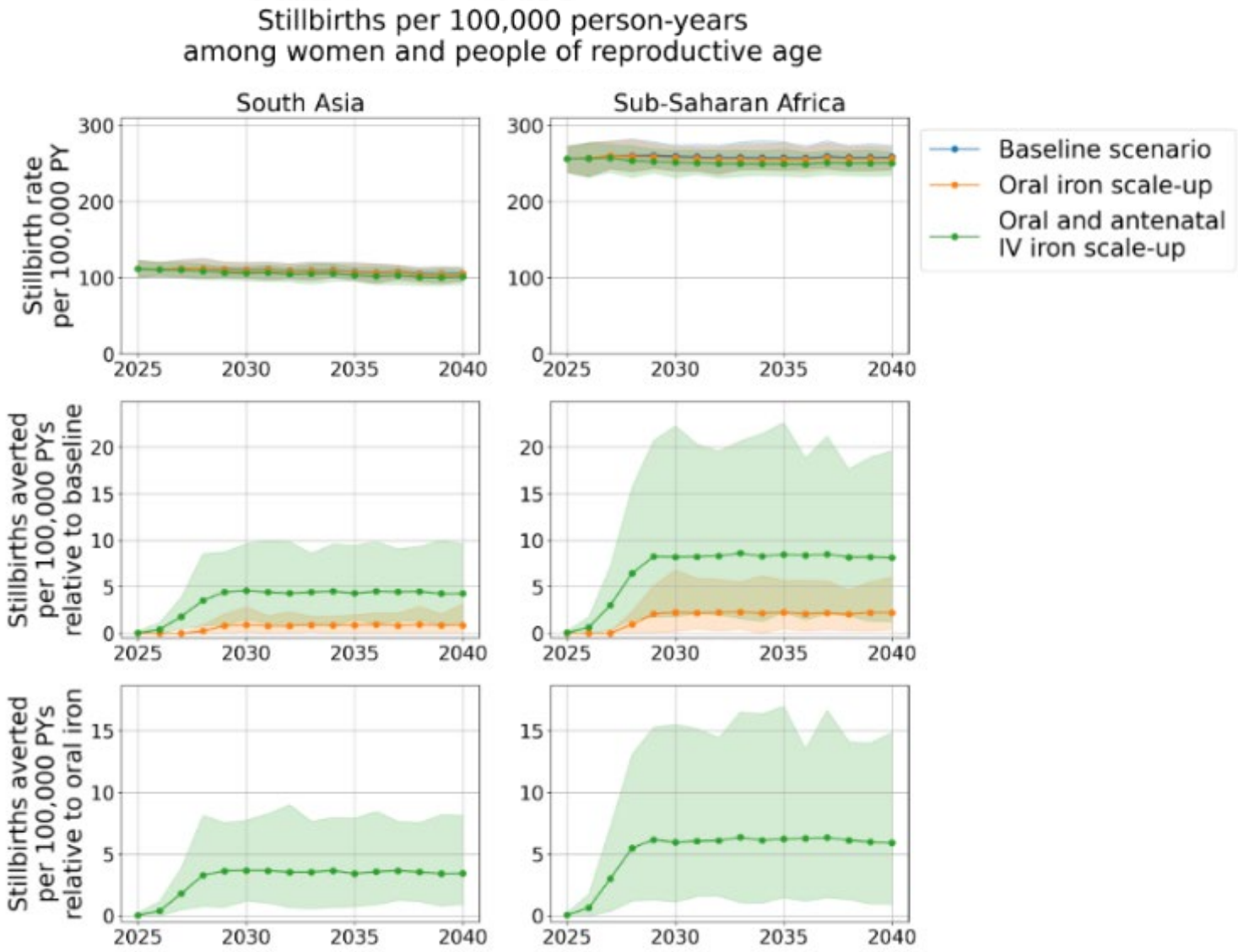
YLDs averted for women or reproductive age and children under 5 *(count space)*



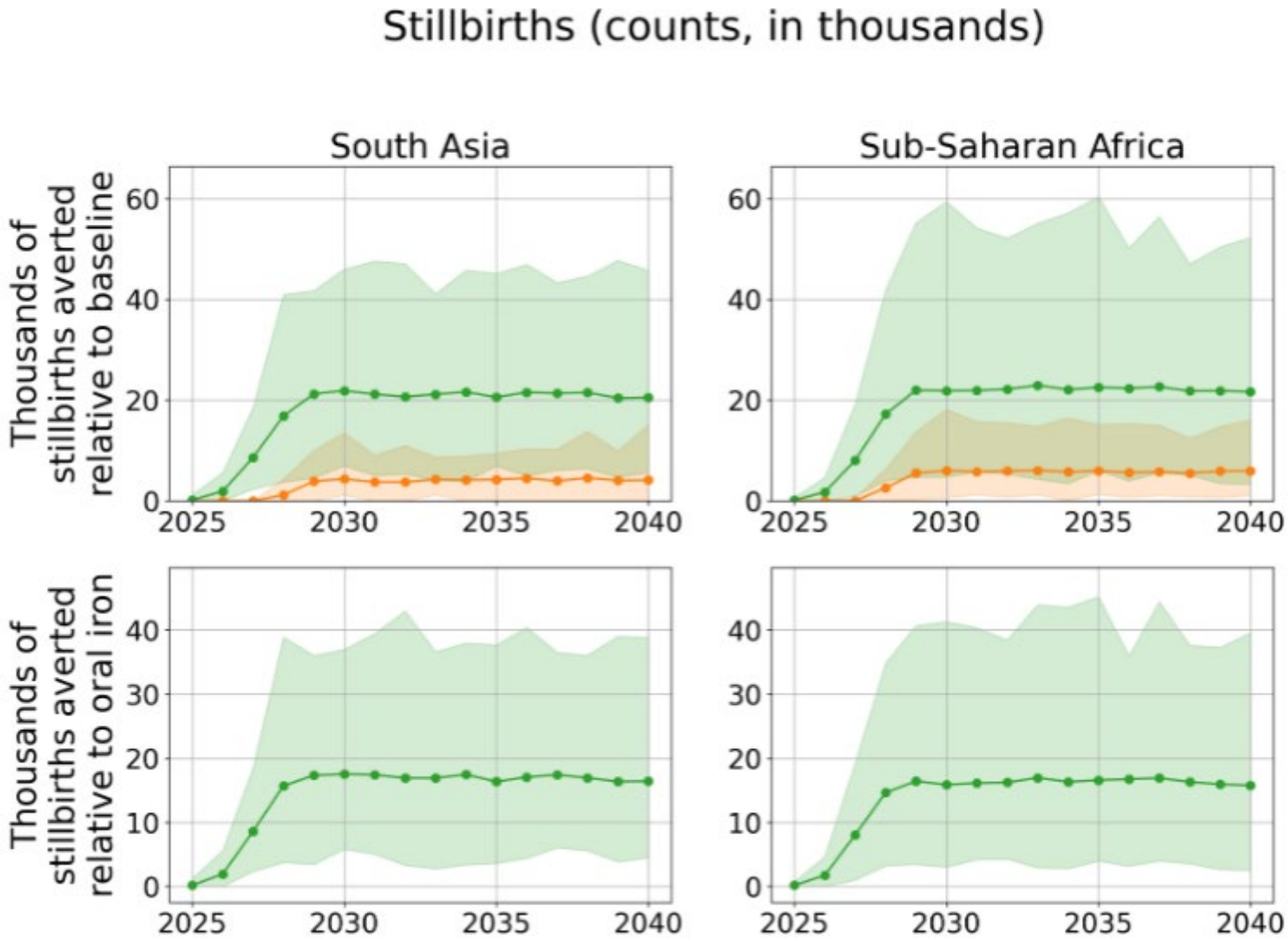
YLLs averted for women or reproductive age and children under 5 *(count space)*



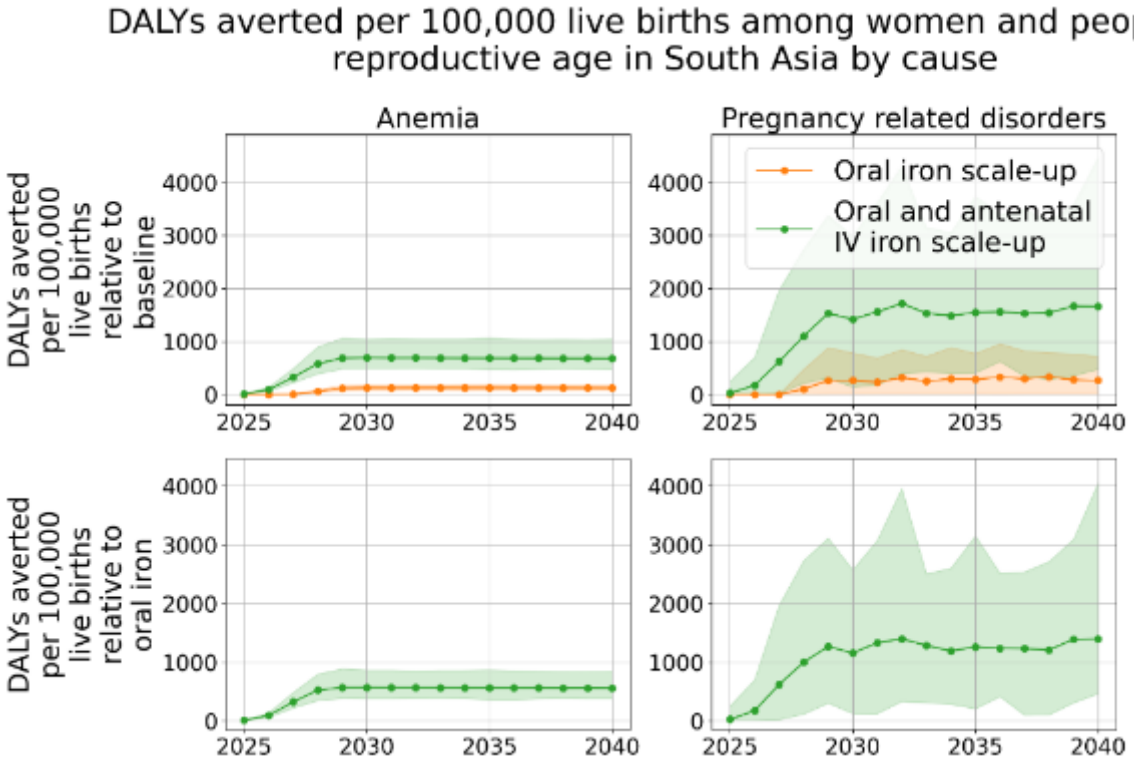
Stillbirths averted *(rate)*

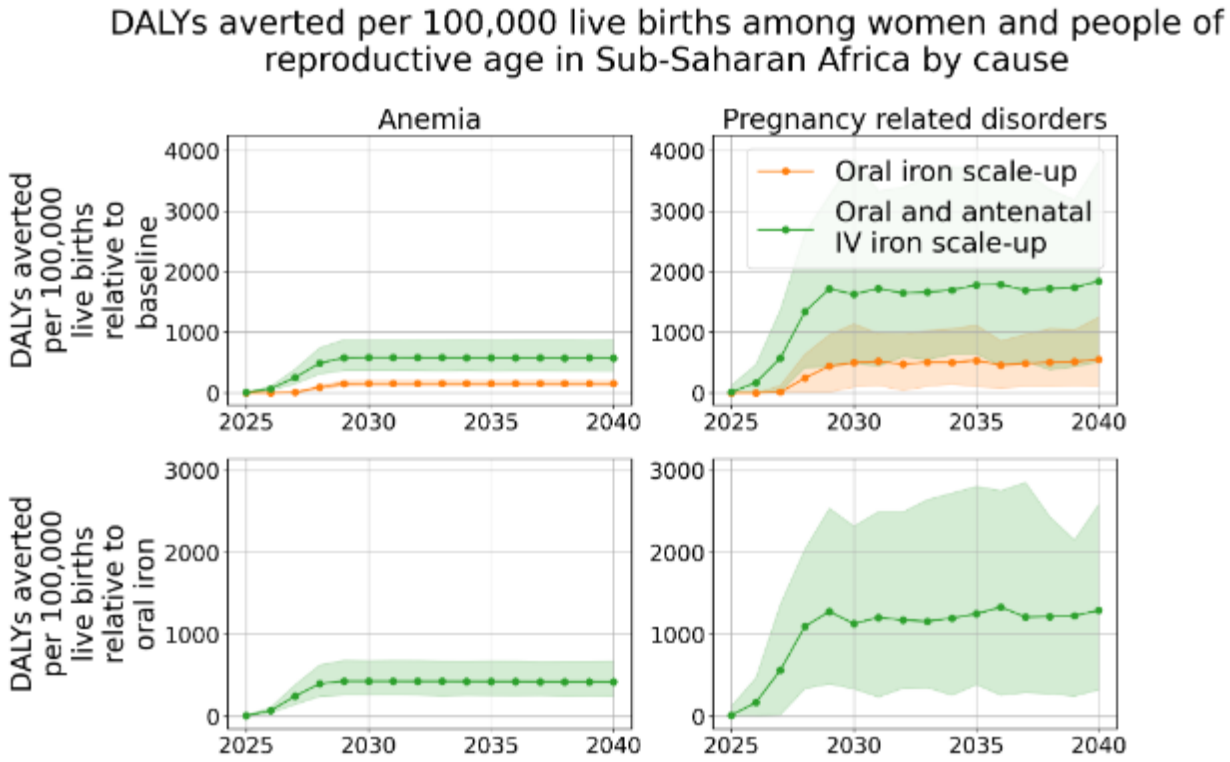


Stillbirths averted *(count space)*



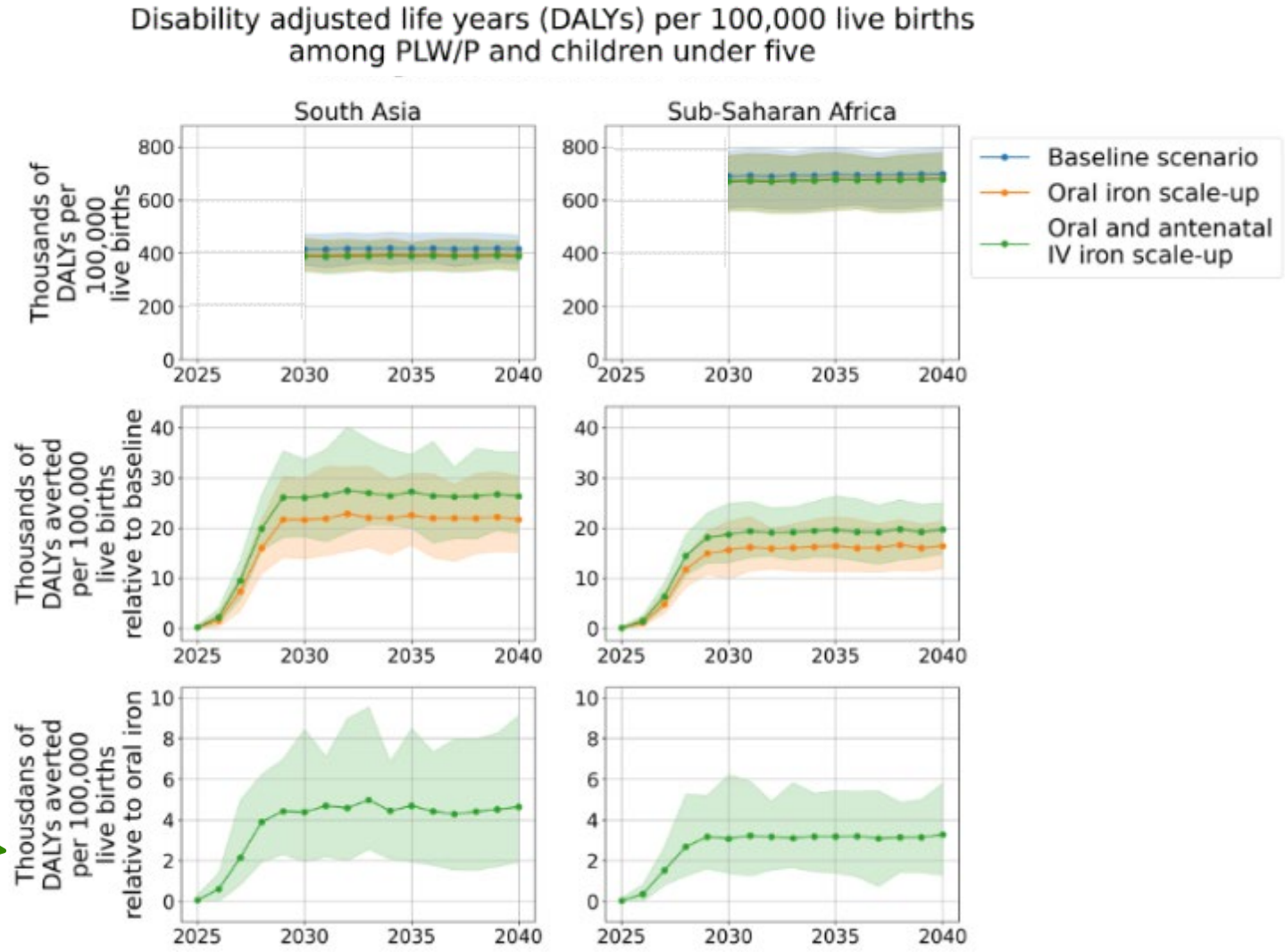
Iron interventions during pregnancy have greater impact on pregnancy related disorders than anemia DALYs





This is approximately 7.1m total DALYs averted in South Asia and 8.7m in Sub-Sharan Africa

Combining the prior results for pregnant and lactating people and children under five, we see a possible total reduction of 20-30 thousand DALYs averted per 100,000 births relative to baseline



This is approximately 8.3m DALYs averted in South Asia and 7.2m in Sub-Sharan Africa