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PAPER TITLE: Small babies, big risks: Global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting

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ABSTRACT

Small newborns are vulnerable to mortality and lifelong loss of human capital. Measures of vulnerability previously focused on liveborn low birthweight (LBW) babies, yet LBW reduction targets are off-track. LBW is caused by two pathways: preterm birth, and fetal growth restriction (FGR) resulting in small for gestational age (SGA). LBW national data are available from 161 of 194 World Health Organization (WHO) Member States and the occupied Palestinian territory, including east Jerusalem (subsequently, throughout the paper, we refer to them as "countries and areas") (82.6%), compared to 103 of 195 (52.8%) national administrative (n=64/195, 32.3%) and research studies data (n=40/195, 21%) for preterm birth, and only eight countries and areas for SGA. New global estimates for 2020 suggest 13.4 million livebirths were preterm, with static rates for the last decade, and 23.5 million were SGA. We estimated prevalence in 2020 for three mutually exclusive small vulnerable newborn types (preterm (PT)+nonSGA, term(T)+SGA, and (PT)+SGA) using individual-level data from 23 national datasets (~165 million live births) and 45 studies in 23 different countries and areas (~0.5 million live births). We found 8.8% (50% credible interval (CrI): 6.8-8.9) of global livebirths were PT+non-SGA (11.8 million CrI: 9.1-12.2 million), 16.4% (CrI: 15.8-18.8) term+SGA (22.1 million,CrI: 21.2-25.4 million) and 1.0% (CrI: 0.9-3.0) preterm+SGA (1.4 million, CrI: 1.2-4.1 million). Over half of the 2.4 million neonatal deaths worldwide in 2020 (55.4%), were attributed to one of the small vulnerable newborn types, of which 72.5% were preterm and the remainder were term+SGA. Analyses from 12 of the 23 countries and areas with national data (0.6 million stillbirths ≥22 weeks gestation) showed around 74% of stillbirths were preterm, including 16.5% PT+SGA and approximately one quarter of term stillbirths were SGA. There are an estimated 1.9 million stillbirths per year, associated with similar vulnerability pathways; hence stillbirths are crucial to add in burden assessments and relevant indicators. Data can be improved by counting every newborn (whether live or stillborn), weighing, and assessing gestational age, and classifying small newborns by the three vulnerability types. Using these more specific types could accelerate prevention and help target care for the most vulnerable babies.

KEY FINDINGS

1. **Small babies, big numbers, slow progress:** preterm birth rates have not changed measurably in the last decade, and low birthweight targets are off track. One in ten livebirths (13.4 million) were preterm ("born too soon") and one in five (23.5 million) were small for gestational age (SGA) ("born too small") in 2020. Of 135 million live births in 2020, 35.3 million (26.2%) were small vulnerable newborns, defined as any baby born preterm, or SGA or both preterm and SGA. Together, these three vulnerable newborn types account for 99.5% of the world's 20 million low birthweight babies. Nearly two thirds (63.9%) of the world's term SGA newborns are in South Asia (14.1 million, 39.2% of livebirths). Preterm birth rates have less regional variation but are also highest in South Asia (13.2%).

2. **Big risks inform targeting for prevention and care:** Mortality risk is highest for preterm birth, especially at lower gestational ages. Newborns who are born both preterm and SGA are less prevalent at 1.0% (50% credible interval: 0.9-3.0%) of births worldwide in 2020 but have even higher mortality risk. SGA including non-LBW newborns has an elevated mortality risk that is lower than that for preterm births, but is more prevalent. Just over half of neonatal deaths (1.4 million) were attributable to small vulnerable newborn types, with most (72.5%) attributable to preterm or preterm with SGA and the reminder to term SGA. Applying these newborn types could accelerate evaluation of mechanisms, diagnostics, and interventions.

3. **Stillbirths are more likely to be preterm and small:** For 12 middle- and high-income countries with individual-level data, around three-quarters of stillbirths were preterm. Around a quarter of term stillbirths were SGA, but this varies by country. Compared to term appropriate for gestational age, the median stillbirth rate ratio was 86.8 for preterm SGA, 24.2 for preterm non SGA, and 5.9 for term SGA, showing a clear association of stillbirth with SVN types. More data are needed, especially from high SGA contexts.

4. **Counting every newborn:** 58% (n=113) of 194 World Health Organization (WHO) Member States and the occupied Palestinian territory, including east Jerusalem have national LBW data, yet only 33% have preterm data. Since >80% of births are now in facilities, routine national data can be improved through increasing coverage of gestational age measurement. In addition to aggregate data, countries and areas need electronic individual-level data on gestational age information, sex, and birthweight to calculate SGA. More investment will enable every baby (including stillbirths) everywhere to be classified by small vulnerable newborn types, improving individual care, tracking of outcomes and accountability for progress.

Introduction

In 2019 there were 8.6 million stillbirths and deaths in newborns, children, and adolescents, of which more than half die during pregnancy or around the time of birth (1, 2), notably almost two million stillbirths in the last three months of pregnancy (3, 4) and 2.3 million liveborn babies dying within their first 28 days (neonatal deaths)(1, 3). Additionally, an estimated 303,000 women died of pregnancy complications, with linked underlying causes in 2017 (5).

The Every Newborn Action Plan set targets of 12 or fewer neonatal deaths per 1000 live births, adopted as Sustainable Development Goal (SDG) 3.2, and for 12 or fewer stillbirths per 1000 total births by 2030, which was not set as an SDG (6, 7). At the half-way point for the SDGs, countries needing the greatest acceleration to meet these targets are in sub-Saharan Africa and South Asia, where risk of death around the time of birth is highest, yet data availability is lowest – the "inverse data law" (8). Lack of a healthy start at birth and global inequalities in care for small, vulnerable newborns is driving these high numbers of deaths for babies around the time of birth (9, 10).

For over a century, newborn vulnerability assessment has traditionally focused on low birthweight (LBW) defined as <2500g (11). LBW is a marker for early death and long-term health, being a foundational metric underpinning lifecourse epidemiology and the Developmental Origins of Health and Disease (12). Globally, an estimated 19.8 million babies were born low birthweight in 2020 (13, 14). There have been global targets for LBW since 1990, none of which have been met and currently the Global Nutrition Plan target aiming for 30% reduction in LBW is very far off track (13, 14, 15). The Global Nutrition Target calls for 30% reduction of LBW by 2030 from a 2012 baseline. The estimated annual rate of reduction is 0.3%, yet would be required to be seven times faster to achieve the target (13, 14).

Importantly, LBW is caused by two underlying pathways – short pregnancy gestation i.e., preterm birth, before 37 completed weeks of gestation (PT) ("born too soon") and fetal growth restriction typically assessed using small for gestational age (SGA) defined as <10th centile of birthweight for gestational age and sex ("born too small") (16). Clinical obstetric and neonatal risk prediction for viability rely primarily on gestational age thresholds. There are more than 20 published scoring models for risk prediction, and most note gestational age is more highly predictive than birthweight alone (17). Importantly, dichotomous classification of LBW at 2500g is not granular enough to understand the continuous gradients of risks for small vulnerable newborns. In addition, historical thresholds may be less relevant given medical advances especially in care of preterm neonates, with most 23-week gestation neonates surviving if neonatal intensive care is available (11, 18).

More accurately identifying types of vulnerable newborns is critical to individual-level care, and to faster progress for primary prevention including delineating causal mechanisms and improving targeted clinical care. Using LBW or preterm alone, also omits consideration of newborns who are term and SGA. Separate measures do not account for overlapping categories, for example, newborns may be both preterm and SGA.

Stillbirths can result from the same pathways affecting liveborn small vulnerable newborns, but are currently not in relevant tracking or burden assessments (19). For instance, the denominator for both LBW and preterm rates is per 100 live births (20). Stillbirths are strongly associated with fetal growth

restriction and hence may be SGA at birth (21). Preterm labour can result in stillbirth and conversely, some stillbirths may result in preterm labour. If measurement and research for small, vulnerable newborns focuses only on livebirths, the true burden, and major effects on women, families, and society are missed (22). Importantly, omitting information on stillbirths from efforts to quantify and address the burden of small vulnerable newborns can be misleading. With better obstetric monitoring of vulnerability in-utero, inductions of labour and caesarean sections increase to prevent stillbirth, yet can increase preterm and SGA rates amongst livebirths (23). The converse may be seen where obstetric care is restricted, for example during COVID-19 pandemic lockdowns some analyses showed reductions in low birthweight and preterm birth amongst livebirths (24), yet omitted stillbirth data, hence potentially misleading given increased stillbirth rates during lockdowns (25).

Evidence regarding preterm births, SGA and stillbirths are each impeded by gaps in data availability and quality (14, 26). However, there have been improvements in data availability and some low-and-middle-income countries (LMIC) have achieved remarkable shifts in the last two decades within routine national data systems, notably for capture of LBW (27). Learning from improvements in these countries' data systems could help to accelerate availability and use of data regarding small vulnerable newborns which is urgently needed in the remaining time to reach SDG targets by 2030.

This paper is part of a five paper Lancet series on small vulnerable newborns. We aim to provide novel, epidemiological data and estimates for all Sustainable Development Goal regions regarding small vulnerable newborns (SVN), to inform faster progress for primary prevention and improved data collection and use. New analyses presented here include:

1. Preterm estimates for 2020, and trends 2010-2020 using population-level aggregate data, are described in detail elsewhere and used here to as an input to the first worldwide SGA estimates.
2. Small vulnerable newborn (SVN) types: Individual-level data analyses and Bayesian modelling for the first prevalence estimates for three mutually exclusive SVN types amongst live born neonates:
   - preterm non-SGA (PT+nonSGA, including AGA and LGA),
   - preterm SGA (PT+SGA)
   - term SGA (T+SGA, including term and post term)
3. Neonatal mortality risk for liveborn SVN types worldwide and multicounty risk of SVN amongst stillbirths; and
4. Measuring better for every baby, everywhere, including stillbirths, based on descriptive analyses of data from 194 World Health Organization (WHO) Member States and the occupied Palestinian territory, including east Jerusalem (subsequently, throughout the paper, we refer to them as "countries and areas").

We also outline implications of better data on these small vulnerable newborn types for guiding basic research, clinical practice, and country programmatic and policy responses.

Preterm and SGA estimates worldwide

The history of data for small vulnerable newborns varies for the different measures, with LBW having over a century of focus, 30 years of prevention targets and now 20 years of national time trends with two rounds of UN estimates (2020 and 2015) (14, 28). Preterm birth rate is a more recent measure even in high-income countries, with more variability in measurement ranging from the gold standard

of early pregnancy ultrasound to more uncertain methods such as Last Menstrual Period, but promising innovations in the pipeline (29, 30, 31, 32, 33). There are now preterm time trends for 10 years (2010-2020), with three WHO estimation exercises for the years 2010 for the "Born Too Soon" report, 2014 and 2020 (9, 26, 34, 35).

In contrast, SGA has had two sets of estimates using two different growth standards, however these were only for some regions, and there are no worldwide estimates or time trends (36, 37, 38). To categorise size for gestational age it is necessary to know the baby's sex, gestational age and birthweight, compared to a standard. Until recently, comparable multi-country estimates were impeded by the lack of an international standard for fetal growth, but this is now available in INTERGROWTH-21st standards (39, 40). These are becoming widely used and were applied in our analyses given the need for international comparisons. In the past, observed differences in human growth were attributed to biological differences, leading to descriptive population-specific charts. However, evidence shows similarities in the growth trajectories in healthy, optimally nourished populations across different contexts worldwide, giving a scientific basis for international, prescriptive growth charts (41, 42, 43).

Preterm birth rate estimates are based on aggregate national data, often from facility based Routine Health Information Systems (RHIS). For the WHO/UNICEF preterm estimates for 2020, 64/195 (32%) countries and areas had nationally representative administrative preterm birth rate data meeting inclusion criteria, compared to 113/195 (57.9%) with administrative data for LBW. Input data for these preterm estimates are shown in Figure 1a. National routine data gaps are most marked across South and South-East Asia and sub-Saharan Africa. Details of data collation, quality assessment and the Bayesian modelling approach used to generate these estimates are provided elsewhere (26, 44).

In 2020, there were an estimated 13.4 million preterm live births or babies "born too soon", constituting one in every 10 newborns (9.9% (credible interval (CrI): 9.1 – 11.2%)) (26) (web annex I and II). Trend estimates for 2010 to 2020 suggest no measurable change in preterm birth rates for most regions and a lack of downward trend especially in the highest burden regions (Figure 2a). Preterm rates vary within most regions, with rates above the global average in some high-income countries such as the United States of America at 10.0% (CrI: 9.6 – 10.4%). For preterm subgroups, globally, 15% of all preterm births are born before 32 weeks (28 and 32 weeks: 10.4% (confidence interval (CI): 9.5 – 10.6%), and before 28 weeks: 4.2% (CI: 3.1 – 5.0%)).

SGA national aggregate data are lacking, with just eight countries reporting on SGA rates and amongst these various growth references were used (27). Hence population-level estimation approaches used for preterm birth or LBW cannot currently be used for SGA (14, 26). Given these gaps, yet the imperative for burden estimation, we estimated overall SGA from the SVN types modelling described below using a Bayesian approach with individual-level data, applying a single common international standard (39, 40) (Figure 2b). We estimated 23.5 (17.4%) million live born babies were born SGA in 2020 (Figure 2b). There was marked regional variation in SGA, with over a third (41.0%) of all newborns in Southern Asia region being SGA, compared to 10.7% in Sub-Saharan Africa and fewer than 10% in other regions. Time trends for SGA could not be estimated due to insufficient data but would be a future priority.

Small vulnerable newborn types worldwide

Given the imperative for addressing overlaps between preterm and SGA, the Lancet Small Vulnerable Newborn series team proposed a novel framework to categorise newborn types based on gestational age (term vs preterm), and size-for-gestational age (SGA vs appropriate for gestational age (AGA), as well as birthweight (LBW vs not low birthweight) (10). The original framework had 6 types, but here we present a simplified grouping based on three mutually exclusive small vulnerable newborn types not including LBW: preterm non-SGA (PT+nonSGA), term SGA (T+SGA), and preterm SGA (PT+SGA). We combined PT+AGA and PT+LGA into (PT+nonSGA) as the mortality risk associated with these types is very similar and prevalence of PT+LGA was low (45, 46, 47) (web annex III). No previous multi-country analyses have been published using these types.

To undertake these analyses, large individual-level datasets were required from around the world. Hence the Vulnerable Newborn Measurement Collaboration was initiated in 2020 to identify datasets meeting inclusion criteria and collate both national datasets (23 countries and areas, 165 million live births) and subnational studies (23 countries and areas, around 500,000 live births) (web annex IV and V). Details of sourcing, data quality, and analyses are given elsewhere (46, 47). The national datasets and some study datasets were analysed by the relevant teams using shared code and standardised tables. Most of the study datasets were analysed by the central study team. Each livebirth was characterised into one of three SVN types, based on: gestational age (preterm, PT, <37 weeks vs term, T, ≥37weeks) and size-for-gestational age according to INTERGROWTH-21st standards (small-for-gestational age, SGA, <10th centile, or nonSGA ≥10th centile) (45, 46, 47, 48). The comparison is term, nonSGA newborns.

Using these data inputs, combined with the WHO/UNICEF preterm birth estimates for 2020, we developed a Bayesian framework to estimate the prevalence of the three SVN types at national level for 195 countries and areas (web annex VI). The Bayesian approach for SVN modelling is outlined in web annex VII. SGA estimates were then derived from the Bayesian modelled estimates of the SVN types.

Overall, of 135 million live births worldwide in 2020, 26.2% (CrI: 25.6-28.6%) were classifiable into one of the three vulnerable newborn types, with 11.8 million (CrI: 9.1-12.0 million) preterm non-SGA, 22.1 million (CrI: 21.3-25.4 million) term SGA, and 1.4 million (CrI: 1.2-4.1 million) preterm SGA (Table 1). The distribution varied by geographical region (Table 1). The highest rates of small vulnerable newborn types are in South Asia where half (52.2%) and sub-Saharan Africa (19.5%) of all newborns are affected, and the lowest in 13.8% of newborns in high-income countries and areas with the low neonatal mortality (Northern America, Australia, New Zealand, Central Asia and European region).

Neonatal mortality and stillbirth risk for small vulnerable newborn types

Neonatal mortality effects

Data from 15 national datasets (125.5 million live births) in high-middle-income settings and 16 subnational, population-based cohort studies (238,000 live births) in low-and-middle income settings with exposure data and linked neonatal survival between 2000 and 2020 were included. National data had high level of completeness for sex, gestational age and birthweight required to estimate newborn types. However, for subnational (ie. Study) data, we used multiple imputation for birthweight and

recalibration of infant weight measured after birth to the time of delivery in view of higher rates of missing birthweight data (web annex VIII-S10) (45, 48, 49).

Since within region variation may be wide in obstetric and newborn care over time, we grouped countries and areas by neonatal mortality rate (NMR) bands using NMRs in the input dataset so that risks were applied to a similar context for estimation (web annex VIII-S11). We used NMR bands that have been previously used for epidemiological and health system analyses (8, 50, 51).

We estimated the relative neonatal mortality risk for each of the three small vulnerable newborn types compared to term non-SGA within each NMR band. The relative risk was highest for those who were preterm, with or without SGA, compared to term nonSGA (Table 2, web annex VIII-S12). Risks associated with being both preterm and SGA were higher than for preterm alone in all mortality settings, table 2). The highest relative risks were observed in the lowest mortality settings, due to the very low mortality risk in the reference/ comparison group (T+SGA). More accurate counting of preterm neonates and deaths at the extremes of viability may also contribute (Table 2).

Over half (55.4%) of 2.4 million neonatal deaths in 2020 (1.4 million) were attributable to small vulnerable newborn types, with 32.9%, 15.2% and 7.2%, respectively attributed to PT-nonSGA, T-SGA and PT+SGA (Figure 4, web annex IX). Northern America region had a highest population attributable fraction of deaths to small vulnerable newborns (68.0%), of which 90.7% were attributed to preterm (web annex IX-S14). Term SGA has a lower relative risk (2.7-3.4) than PT+nonSGA (4.0-11.6, table 2)), but given high SGA prevalence, does account for 15.2% of attributed mortality globally, and 21.7% in South Asia, where over half of the world's term SGA babies are born (Table 2).

Stillbirth effects

Stillbirth is an extreme outcome of the small vulnerable newborn etiological pathways, and small vulnerable babies may die before or during labour and be associated with preterm birth. There are an estimated 2.0 million late gestation stillbirths (at ≥28 weeks of gestation) worldwide each year, and the overall burden including all stillbirths from ≥22 weeks of gestation is even higher. Despite this large burden, most of which is preventable, there has been limited attention to stillbirths until recently and progress in reducing them has been slow (4, 52). Stillbirths have not been included in most burden estimates and indicators for small babies including LBW and preterm birth. Few previous analyses have estimated gestational age distribution for stillbirths and contribution of suboptimal fetal growth to stillbirths using comparable multi-country data. We sought to close these gaps using stillbirth data from 12 out of 23 high and upper-middle income countries and areas participating in the Vulnerable Newborn Measurement Collaboration, including 605,557 stillbirths after 22 weeks of gestation (53) (Panel 1, web annex X).

In this analysis, three-quarters of the stillbirths were preterm. Around a quarter of term stillbirths were SGA, although this varied by country. The median relative risk for association of stillbirth with PT+SGA was 86.8, PTnonSGA was 24.2, and 5.9 for T+SGA, compared to T+nonSGA as a reference. Future analyses with data from lower income contexts would be important, notably South Asia given very high SGA prevalence.

Implications for programmes

Our findings show that in 2020 around one in four live born newborns worldwide (28.3%) were estimated to have at least one small vulnerable newborn type, which is a larger number at risk then using the LBW threshold alone. Globally 13.4 million of these were preterm and 23.5 million term SGA newborns (Figure 4). South Asia has higher rates of preterm birth than the global average and

additionally very high rates of SGA, accounting for 25.6% of global live births, but half (53.3%) of all small vulnerable newborns. This excess of SGA is multi-factorial, including inter-generational (ref Lancet SVN paper 3).

Amongst the 2.4 million neonatal deaths worldwide in 2020, small vulnerable newborns were estimated to be 1.7 million (66.7%) of which the majority (around 1.0 million) were preterm. Globally the attributed deaths (55.4%) are lower, with preterm births accounting for over 73% of neonatal deaths attributed to small vulnerable newborn types. In the highest mortality settings, there is still an excess of deaths in non-small newborns, but in regions with lower levels of mortality, the attributable fraction of deaths is higher for small vulnerable newborn types.

Neonatal mortality is only part of the overall burden associated with SVN types. Small babies are at greater risk of complications throughout their life-course including stunting, non-communicable disease risk, long-term disability, and reduced learning potential (Figure 4). South Asia's exceptionally high SGA rates has many implications, including fuelling the epidemic of non-communicable conditions in later life, particularly diabetes and hypertension.

At individual-level, more investment is needed in closing major survival gaps for newborns in low-income settings. Most of the progress in reducing neonatal deaths in middle and high-income settings can be attributed to improved neonatal care (54), and there is potential to save 742,700 lives per year in low and middle income countries and areas with more investment in small and sick newborn care, including respiratory support and other care for preterm neonates (55).

Primary prevention is crucial, given big numbers, high risk and slow progress in reduction; yet few countries and areas have shown convincing reductions. With high-income, and many middle-income countries and areas reaching the thresholds of viability, more progress for survival, and importantly, for disability-free survival, will be increasingly dependent on primary prevention. Research on mechanisms, diagnostics and interventions may benefit from more specific evaluation against these three specific vulnerable newborn types (ref Lancet SVN paper 3).

Including stillbirths is crucial to assessing the full loss of human capital due to small babies as the majority of these 2.0 million annual stillbirths may occur preterm, some also associated with sub-optimal growth in-utero (fig 4).

Measuring better for every newborn, everywhere

Improving aggregate data in routine systems

Data availability in national routine systems has increased over the last two decades, notably with higher facility births rates and expanded data systems, including both health information systems and birth registration (27). Of 195 countries and areas, 117 have stillbirth rate data, but still with reliance on surveys (3, 4). For LBW data, 113 countries and areas have national routine data included recent estimates (14). All babies born in health facilities should have a birthweight recorded, and hence it should be possible to collate national LBW data. In most regions there is a gap between countries and areas with more than 80% facility births, and those reporting LBW data usable for national estimates, and this is most notable in South Asia where most countries and areas have high facility birth rates, yet few have useable national LBW data (Figure 5).

National Routine Health Information Systems collect aggregate data through tallies at the facility level, for example, from labour ward registers counting each woman and her baby. Routine birthweight data in labour ward registers have been shown to be have good completeness and be valid, with little

heaping, which is even less with digital scales (56). Aggregated data are collated at facility, district, and national level in electronic platforms such as DHIS-2, which is operational in over 80 low- and middle-income countries and areas. In countries and areas with high levels of facility births and functional national electronic data systems, closing data gaps should be achievable (fig 5). In countries and areas with low facility birth rates, weak routine information systems, for example in humanitarian contexts, other strategies may be needed.

Preterm birth data has more gaps, with only 64 out of 195 countries and areas having national routine data meeting inclusion criteria for the latest WHO/UNICEF preterm birth estimates (26). Whilst first trimester pregnancy ultrasound dating is the gold standard, sonography up to 22-24 weeks is considered acceptable (57, 58). Recent innovations in late pregnancy ultrasound may increase accuracy of post-24 weeks dating (32, 59). Using the indicator of four antenatal care (ANC4) contacts, large data gaps were evident in all regions between ANC4 and availability of national data on preterm birth rate (Figure 6). ANC4 is very high in almost all countries and areas and closing these gaps requires access use of dating ultrasound technology. Improvements in gestational age data are important for both individual clinical care and improving national routine preterm birth data.

Regarding SGA data, almost no national data were available in the public domain, with only eight countries reporting this, further impeded by variation in standards for SGA classification (27). For countries and areas already collecting data on both LBW and preterm birth, closing the gap for SGA data should be feasible (Figure 6) and innovations may help, e.g. electronic medical record (EMR) systems that auto-calculate Z-scores and percentiles, software applications or smartphone based apps (60).

Survey data collected by three to five-yearly household platforms such as DHS, are still used in lower income countries and areas for LBW national estimates and will continue to be important in countries and areas with low facility births or humanitarian emergencies. Whilst these survey birthweight data have biases, notably missingness and heaping (61), some can be adjusted in a standardised way using individual-level datasets (28). Current survey tools are not sensitive for accurate gestational age information, but there is potential for improvement, notably if women have and know their gestational age (62). In view of the shift to facility births in all contexts, investment in improving routine health information systems data for small babies could be the most sustainable to ensure high quality, timely data for every birth.

Improving and using individual-level data for SVN types

Improving SVN data will require counting every baby, whether live or stillborn, with information on birthweight, sex, and gestational age. Information systems require aggregate data at national level, but it is crucial that this can be linked to individual-level data, ideally electronic, for example on maternity or newborn care wards. Having multi-country standardised electronic data platforms is key for tracking individual care, for quality improvement and linking for longer term outcomes. Such systems enable inbuilt data checks and timeliness to accelerate action to improve outcomes for all babies – live and stillborn.

Assessing size-for-gestational age assessment has additional challenges and is influenced by the choice of standards, which may result in apparent varying of SGA rates (63). Differences observed in growth patterns in LMICs arise largely due to socioeconomic and health constraints on fetal growth, such as maternal nutritional status, pregnancy morbidity and environmental exposures. To compare across multiple populations requires an international standard (43), of which the most widely used is the INTERGROWTH-21st project (39).

When this Lancet series was planned, we had proposed six newborn types, including a birthweight dimension (LBW vs non-LBW) as well as preterm birth and SGA (10). The types have been simplified by focusing on three SVN types in this paper, noting that 99.5% of LBW newborns are in the three categories of PT, SGA or PT+SGA. It is justifiable to combine preterm AGA and preterm LGA since the mortality risks are very similar (web annex III figure E1, E2) (64). Since short length of gestation is the strongest predictor of mortality risk and longer term adverse neurodevelopmental outcomes, (45, 65), splitting the preterm categories into subgroups based on maturity could provide useful additional information for both policy and programming and individual care. Further categorisations of severity of SGA e.g., <3rd centile could be informative (66). Whilst the smallest newborns have the highest mortality risk, large for gestational age (LGA) is increasing in prevalence and may in some settings be associated with an increase in risk; it could also be included to provide a more complete overview (64). More work is still needed to better understand and link these types, including LGA, to life-course outcomes. More granular types, with more splits of gestational age may be useful for specific questions, notably research on aetiological pathways or interventions, but are likely to be too complex for programmatic use. In addition, other data on both causes and outcomes will be needed to inform action. A lack of individual level data meant that risk ratios of mortality were unadjusted for confounders. This is likely to have led to biases in the calculation of PAR using Levin-type formulas instead of alternatives(67) which is an acknowledged limitation.

Research gaps for better measurement including long-term consequences

Improving quantity, quality, and use of SVN data will require information systems that count every baby and ensuring data from every facility flows into national aggregate data, with interoperability so that individual-level datasets can be linked to track later outcomes such as mortality or disability. Recent innovations are available for gestational age measurement, but more are needed, with evaluation of cost and implementation feasibility at scale, as well as accuracy in different populations. Implementation research in various contexts is required to inform efforts to improve data quantity, quality, and flow to enable SVN type characterisation at individual, national, and global level. A parsimonious standard dataset is needed for every newborn at birth, and to track quality and outcomes for care of small and sick newborns (68). As well as improving data availability and data quality, more focus is required on increasing data use at all levels, including building capacity to recognize implausible data, and reporting gaps for example due to missing the smallest babies. Evidence regarding the full impact of SVN including longer-term life-course outcomes and impact on human capital could be generated using these more granular SVN types as exposures at birth and linking to routinely collected data on longer term mortality, morbidity, education, and socio-economic outcomes.

International approaches to assess size for gestational age include the use of either a prescriptive or descriptive approach (69). Prescriptive fetal growth standards are the only option that enables international comparisons, whereas descriptive charts are commonly used to produce a reference based on anthropometry of a given population at a particular time and place, such as a hospital, region or country, with varying risk factor exposures and access to care (69, 70) (71).

Studies to examine aetiological pathways and basic mechanisms could benefit from measuring these specific SVN types, rather than crude markers, such as LBW. The next paper in this series examines current evidence and notes the challenges of inconsistent outcomes, as well as multiple exposures including nutrition, infectious and obstetric conditions, as well as congenital anomalies (72).

Intervention research would also gain from assessing these more specific SVN types and including stillbirths as an outcome where relevant (73). For example, most studies of insecticide-treated bednets in pregnancy measured LBW yet omitted outcomes of preterm, SGA or stillbirths.

Conclusions

In every country worldwide, big numbers of small vulnerable newborns each year, almost 35 million, contribute disproportionately to early deaths and long-term loss of human capital. Vulnerability for small babies was identified centuries ago, and for the last 30 years the world has set – and missed – global targets for LBW reduction. These more specific small vulnerable newborn types enable advancing beyond the crude marker of LBW, now measuring the two underlying pathways of preterm birth and fetal growth restriction. Stillbirths also need to be included in counting. Using these small vulnerable newborn types, we can better inform individual-level care, enable more precise research on aetiological pathways and interventions, and hence accelerate unacceptably slow progress on primary prevention, improving outcomes for every baby, everywhere.

ABBREVIATIONS

AGA	Appropriate for gestational age
ENAP	Every Newborn Action Plan
GA	Gestational age
LBW	Low birthweight
LGA	Large for gestational age
SDGs	Sustainable Development Goals
SVN	Small Vulnerable Newborns
PT	Preterm birth
SGA	Small for gestational age

DECLARATIONS

Ethics and consent to participate

The Vulnerable Newborn Measurement Collaboration was granted ethical approval from the Institutional Review Boards of the London School of Hygiene & Tropical Medicine (ref: 22858) and Johns Hopkins University. All collaborators received local ethical permissions for their data where relevant (details in web annex IV).

Consent for publication

Not applicable.

Availability of data and material

Data sharing and transfer agreements were jointly developed and signed by all collaborating partners. Pooled summary tables generated will be deposited online at the time of publication at https://doi.org/10.17037/DATA.00003095 with data access subject to approval by collaborating parties.

Competing interests

To complete after checking with all authors re competing interests.

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Authors' contributions
The Vulnerable Newborn Measurement Collaboration was conceptualised by JEL and REB. Descriptive analyses of the pooled datasets were undertaken by LSI, YO, EH, DE, EOO, MD, and Bayesian modelling, and mortality risk estimates by EB with statistical oversight by EOO and epidemiological oversight by HB and JEL, plus ACL for SGA and PAR including review by MS and REB. ABM, CH and EB were part of the WHO/UNICEF estimation group for preterm birth and LBW. The manuscript was drafted by JEL with HB, EOO and REB. All authors reviewed and helped revise the manuscript and agreed the final version. The content of this paper represents the individual author's positions and does not constitute the official position of any of the relevant institutions.

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FIGURES AND TABLES

Table 1: Estimates of prevalence for three small vulnerable newborn types by region for 2020 per 100 livebirths

Regions (SDG)	Preterm nonSGA		Term SGA		Preterm and SGA		Total any SVN type	
	% [50% credible intervals]	Number (thousands) [50% credible intervals]	% [50% credible intervals]	Number (thousands) [50% credible intervals]	% [50% credible intervals]	Number (thousands) [50% credible intervals]	% [50% credible intervals]	Number (thousands) [50% credible intervals]
Latin America and the Caribbean	8.1 [7.9, 8.3]	796.3 [770.3, 809.9]	7 [6.1, 8.6]	689.3 [597.6, 844.2]	0.8 [0.6, 1]	73.8 [60.2, 99.8]	15.9 [15, 17.5]	1559.4 [1467.7, 1714.3]
Eastern Asia, South -Eastern Asia, Oceania+	6.6 [6.4, 6.8]	1673.7 [1617.3, 1706.8]	7.3 [5.9, 9.9]	1831.5 [1478.8, 2507.4]	0.6 [0.5, 0.8]	155.1 [122, 211.5]	14.5 [13.1, 17.2]	3660.3 [3307.6, 4336.2]
North America, Australia, New Zealand, Central Asia, Europe	7.2 [7, 7.4]	951.6 [921.2, 969.4]	5.9 [4.1, 8.6]	774.7 [542.2, 1126.9]	0.7 [0.5, 0.9]	87.6 [69.7, 118]	13.8 [12, 16.5]	1813.8 [1581.3, 2166]
Southern Asia	11.2 [3.9, 12]	4040 [1424.9, 4335.8]	39.2 [35.3, 43.1]	14137.4 [12730.8, 15572.7]	1.8 [1, 9.1]	658.5 [362.7, 3273.6]	52.2 [48.3, 56.2]	18835.9 [17429.3, 20271.2]
Sub-Saharan Africa	8.7 [8.5, 8.9]	3395.2 [3283.1, 3460.2]	9.9 [8.1, 13.4]	3856.7 [3137.6, 5182.7]	0.8 [0.6, 1.1]	314.2 [249.1, 426.3]	19.5 [17.6, 22.9]	7566 [6846.9, 8892.1]
Western Asia and Northern Africa	8.3 [8, 8.5]	968.8 [937.4, 991.5]	7.2 [4.2, 11.7]	840.6 [493, 1359.4]	0.8 [0.6, 1]	89.6 [66.9, 120.9]	16.3 [13.3, 20.8]	1899 [1551.3, 2417.7]
Global	8.8 [6.8, 8.9]	11825.5 [9111.1, 12003]	16.4 [15.8, 18.8]	22130.2 [21318, 25382]	1 [0.9, 3]	1378.8 [1201.2, 4093.1]	26.2 [25.6, 28.6]	35334.5 [34522.2, 38586.2]

+ excl. Australia New Zealand) CI= Credible interval

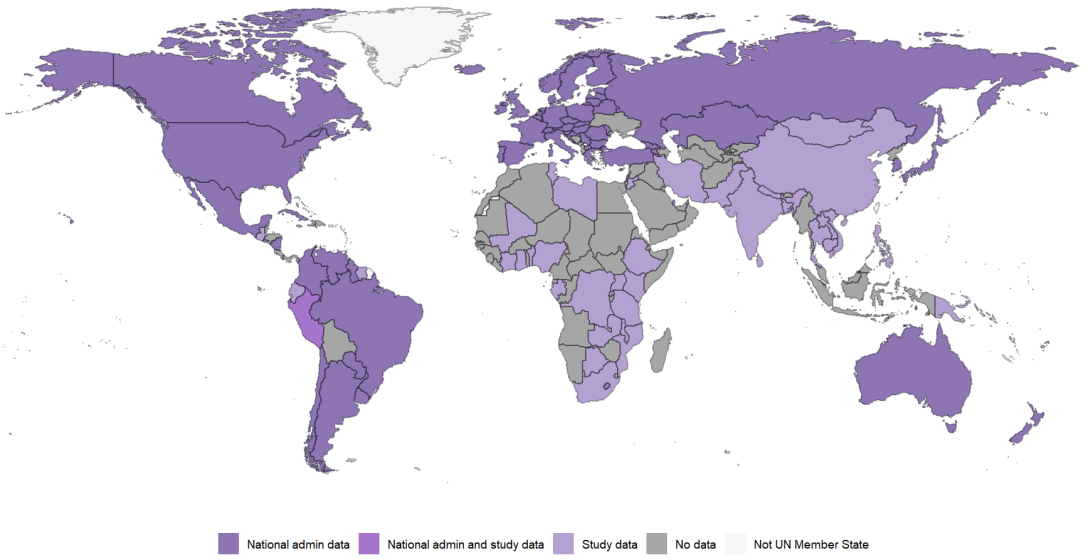
Table 2: Neonatal mortality relative risk for three small vulnerable newborn types by neonatal mortality rate group

NMR	Number of countries and areas in NMR group (2020)	Input datapoints		Neonatal mortality rate per 1000 Livebirths	Neonatal mortality relative risk (RR)		
Deaths per 1000 LB				T+nonSGA (Reference group)	PT+SGA	PT+nonSGA	T+SGA
				(median, IQR)	(median, IQR)	(median, IQR)	(median, IQR)
30 to <45	15	6 subnational studies		13.8 (7.5, 14.5)	12.4 (8.8, 18.7)	11.6 (5.7, 19.9)	3.4 (2.2, 4.9)
		100,913 livebirths	4,016 deaths				
15 to <30	48	5 subnational studies		10.1 (7.3, 11.6)	12.7 (6.0, 14.4)	10.6 (5.1, 11.8)	2.7 (2.5,2.7)
		40,339 livebirths	1,078 deaths				
5 to <15	65	5 subnational studies		6.3 (3.4, 7.0)	10.4 (7.3, 39.6)	4.0 (2.6, 11.7)	2.7 (1.5, 4.1)
		96,860 livebirths	1,247 deaths				
		2 national datasets					
		26,906,355 livebirths	182,454 deaths				
<5	67	13 national datasets		0.6 (0.4, 0.6)	76.8 (70.3, 89.1)	36.5 (32.7, 40.9)	5.9 (4.6, 6.8)
		96,020,388 livebirths	286,777 deaths				

See web annex VIII for details

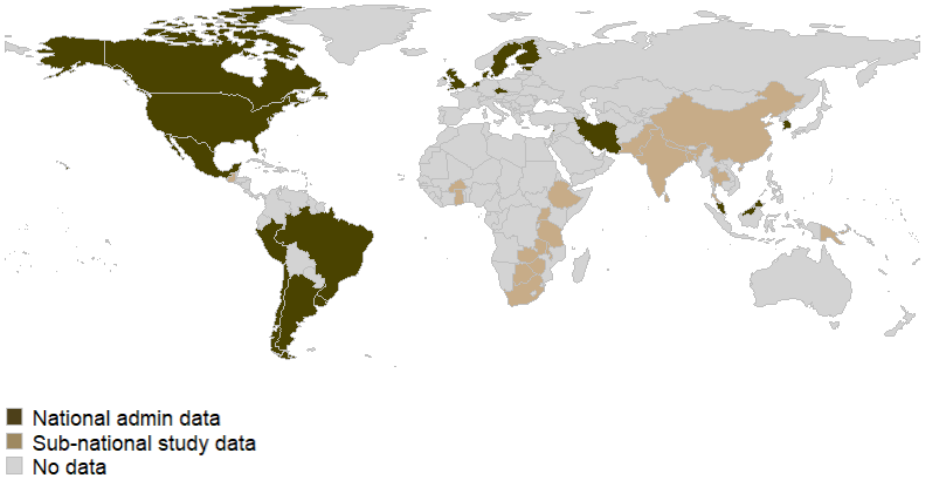
Figure 1: **Input data for vulnerable newborn types, regional and global estimates**

a. Aggregate data available for national rates of preterm birth used in UNICEF/WHO 2020 estimates



Web annex IV for details. Source: (26)

The boundaries shown on this map does not signify any official endorsement of borders, or the legal status of any country.



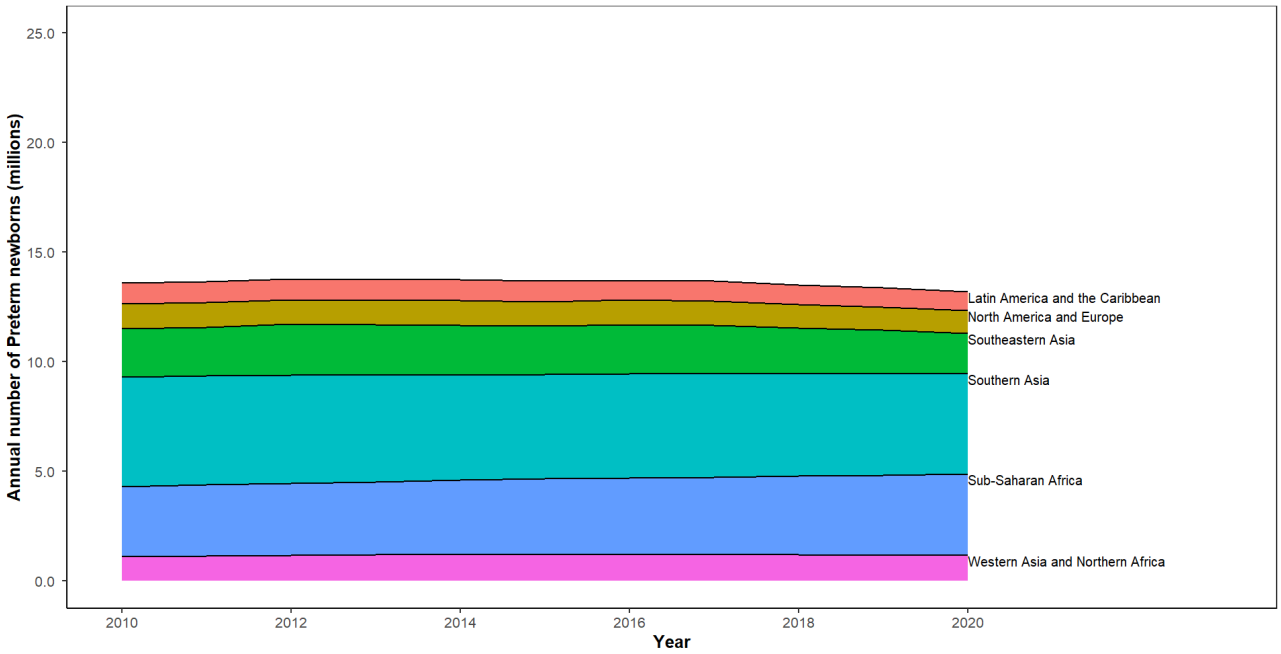
b. Individual-level data available for estimation of SGA and Small Vulnerable Newborn types

National data available from 23 countries and areas (165 million livebirths), study or subnational data from 23 countries and areas (0.5 million livebirths). In total 43 countries and areas contributed data as Argentina, Brazil and Mexico had both national and subnational data sets. See web annex VI for details. Source: (46, 47)#

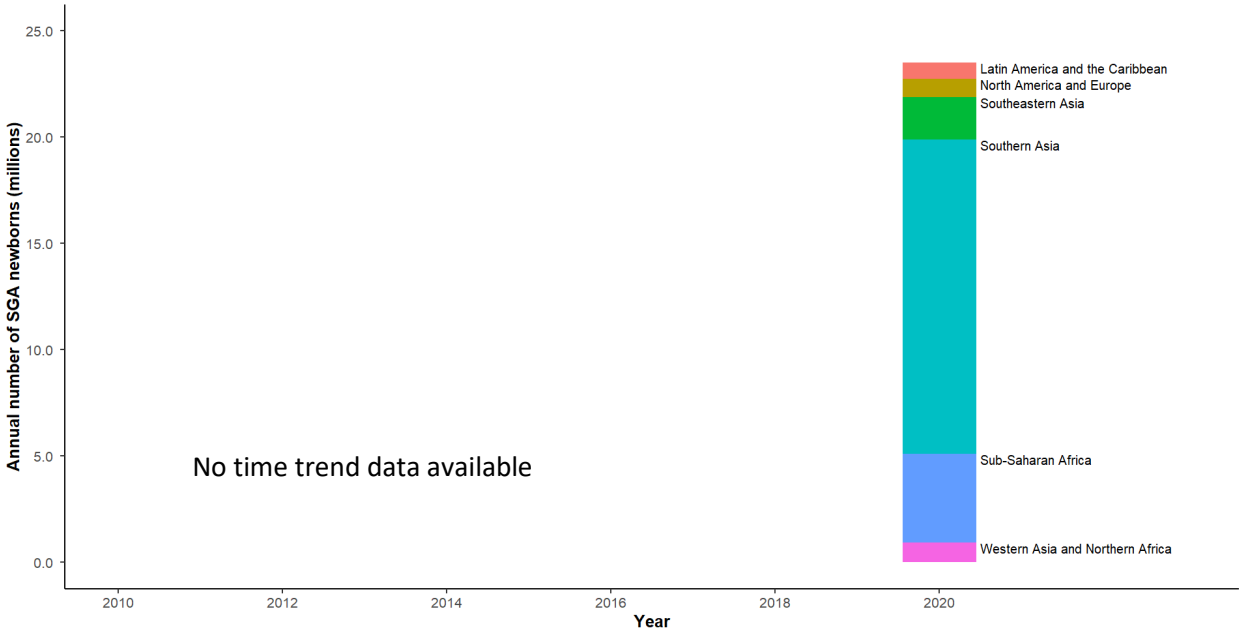
The boundaries shown on this map does not signify any official endorsement of borders, or the legal status of any country.

Figure 2: **Preterm birth and SGA: regional, and global estimated numbers**

a. Preterm birth numbers by region for 2020, with trends 2010-2020, based on WHO/UNICEF estimates

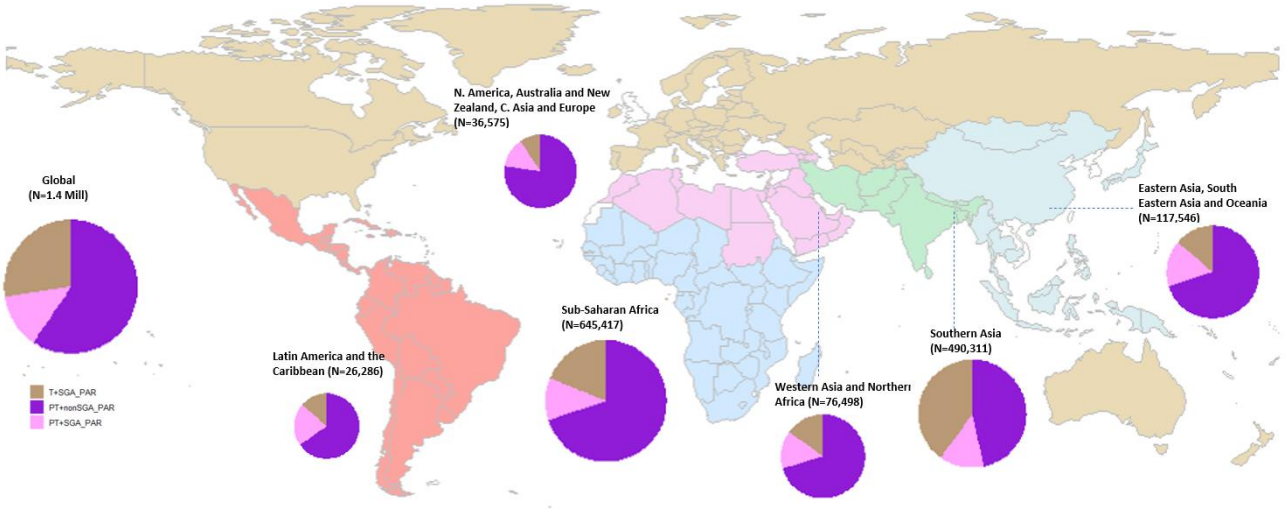


b. Small for Gestational Age estimated numbers by region for 2020



Reference: (26, 44). Webannex II. Web annex V - VII

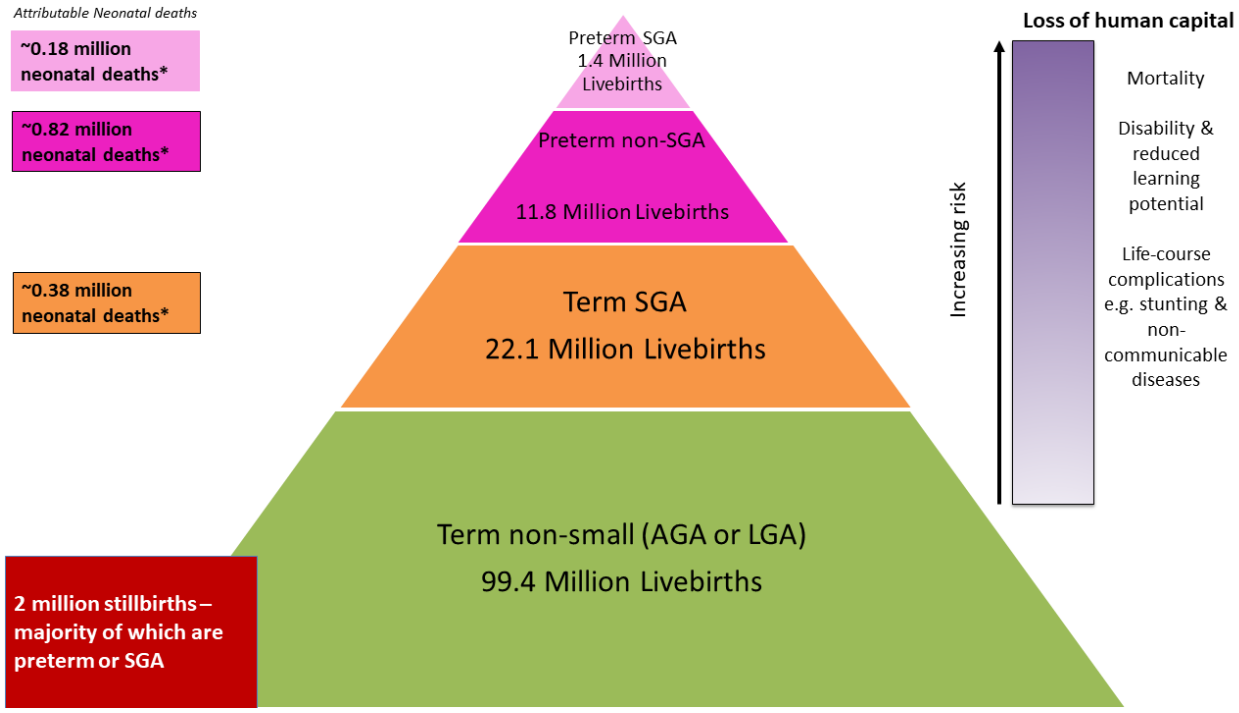
Figure 3: Distribution of attributable neonatal deaths by three small vulnerable newborn types by **Sustainable Development Goal regions**



The map is coloured to show Sustainable Development Goal regions. The areas of the pie charts are proportional to region-specific numbers of attributable deaths. Each pie charts presents neonatal deaths by attributable vulnerable newborn types. The boundaries shown on this map does not signify any official endorsement of borders, or the legal status of any country.

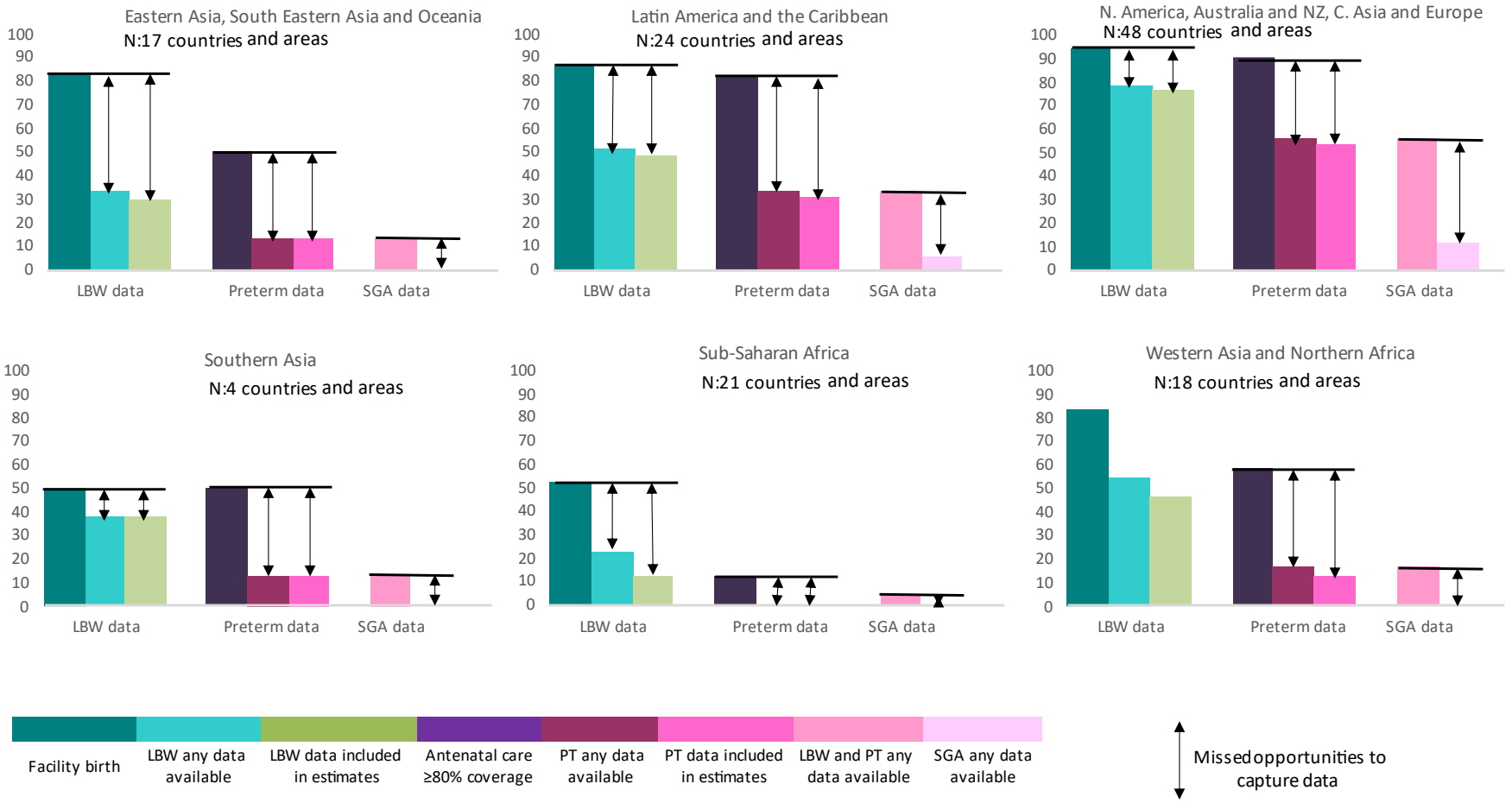
See web annex IX-S13 for details.

Figure 4: Population level implications of the burden of small vulnerable newborns and neonatal mortality by SVN type



See web annex IX for details

Figure 5: Missed opportunities for improved data on LBW, preterm birth and SGA, based on national data for 195 countries and areas by region

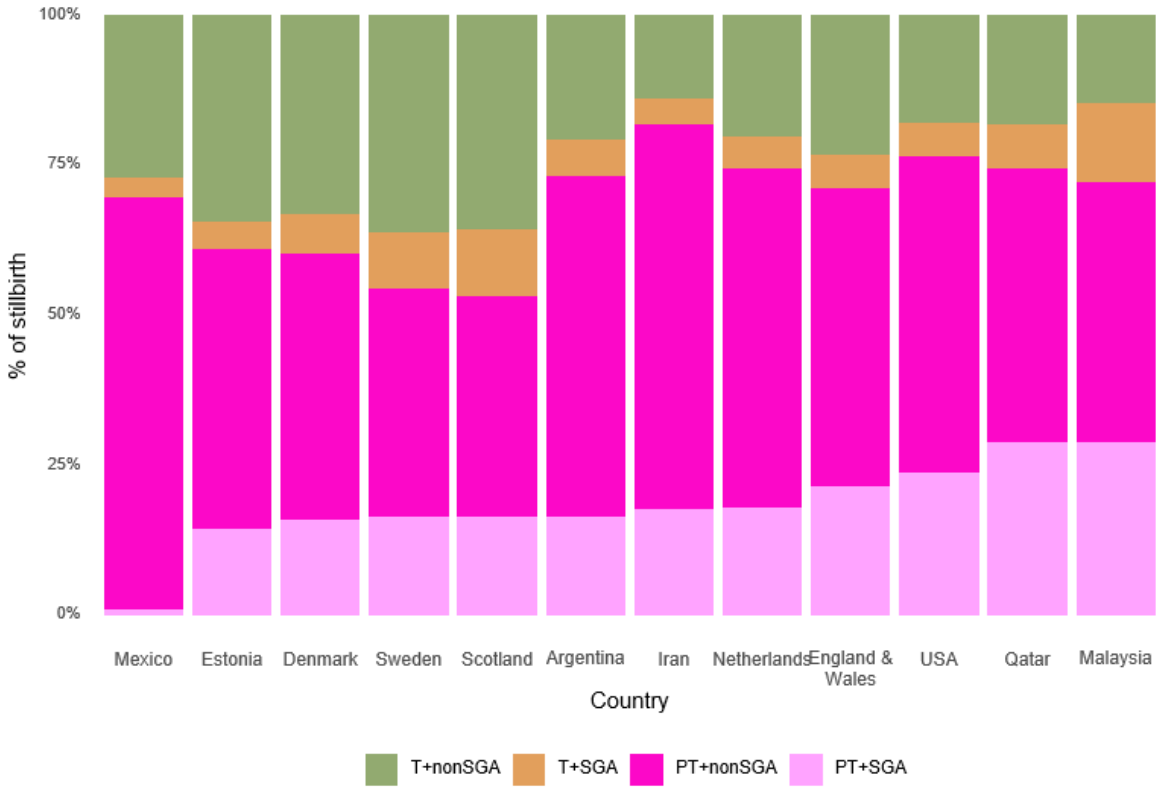


N: number of countries with >80% facility births by region

No national SGA data were available from the Asian or African regions. See web annex XI for details

Panel: Stillbirths and vulnerability related to preterm and/or SGA

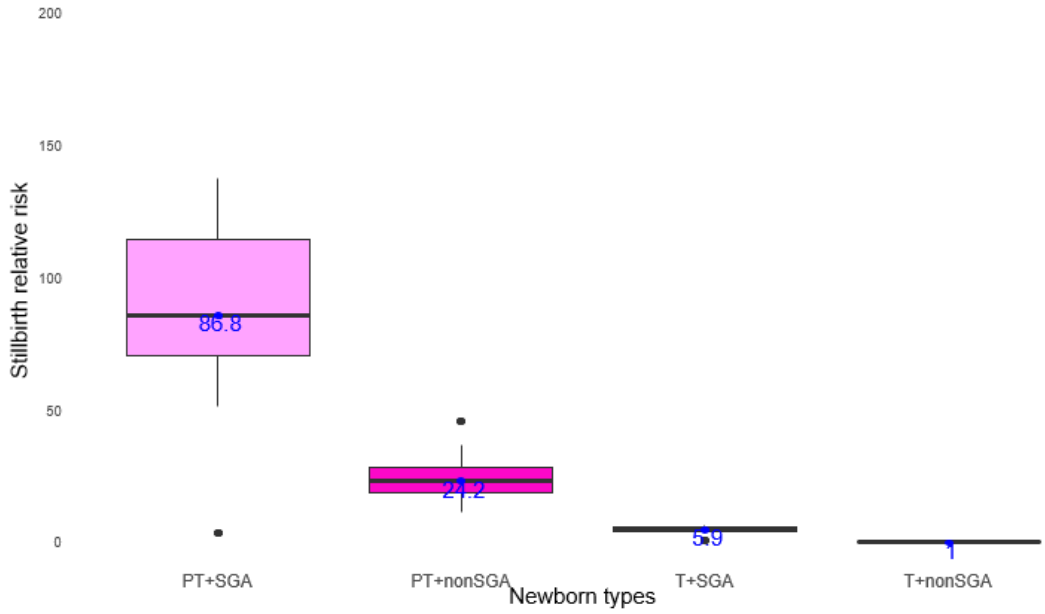
Figure P1: Stillbirth rates by vulnerable newborn type



Methods: We included 605,557 stillbirths beyond 22 weeks gestation and 119,644,788 total birth born between 2000 and 2020 from 12 countries and areas in Latin America, Europe, North America, Western Asia, South-east Asia (53). Some countries and areas have variation in their threshold for stillbirth definition, for example, at 20 or 23 weeks of gestation, but these analyses used 22 weeks and standard measures including standards for size by gestational age and sex according to INTERGROWTH-21st project. All births were classified according to the three SVN types (PT+nonSGA, T+SGA, PT+SGA) or the reference (T+nonSGA).

Results: Around three quarters of included stillbirths were born preterm, with a fifth being PT+SGA (Figure P1). Approximately one quarter of term stillbirths were SGA, although this varied by country. The median rate ratio (RR) for the association of stillbirth with SVN types was highest for preterm (PT+SGA: RR=86.8 (IQR:71.9 – 115.7)) or PT+nonSGA: RR=24,2 (IQR:20.0 – 29.3) compared to those born T+nonSGA (Figure P2). The risk was highest for the most preterm (<28 weeks: RR=146.3(IQR, 110.7, 200.7)) and (28-31 weeks: RR=59.4(IQR, 49.9, 66.9)) but remained raised even in the late preterm period 34-36 weeks (RR=7.7(IQR,6.9, 8.6))). Those SGA remained at increased risk of stillbirth even after term (RR=5.6 (IQR,2.8, 13.8)) (Figure S14).

Figure P2: Stillbirth relative risk by vulnerable newborn type for 12 countries and areas (n=605,557)



Note: Box and whisker plots show median relative risk and IQR

Implications: Our analysis has strengths, including high data quality and comparability of standards and approach, but included data were all from high and upper middle-income countries and areas; more data are needed from other contexts. Improved data on timing of fetal death in relation to gestational age, and the relative contribution of fetal growth restriction to these deaths could inform interventions now and in future research towards ending preventable stillbirths. Improved data use at individual and population level is possible now.

See web annex X for details