Lancet series: Small Vulnerable Newborns 1

Small vulnerable newborns – big potential for impact

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Key messages

1. Newborns who are preterm, small for gestational age (SGA), or have low birth weight (LBW), account for most neonatal deaths worldwide. These conditions are also associated with stillbirth and life-long health adversities among those who survive their early weeks.

2. Prevention of preterm birth, SGA, and LBW would lead to major advancements in global health and economic and social development. However, there has been little progress in prevention, despite several globally expressed commitments in the past 30 years. This can be explained by the inadequate response of the global community to four challenges, consisting of problem definition, framing of the problem, coalition-building, and governance. Major impact is possible with adequate response to these challenges.

3. To facilitate an improved problem framing and response, we propose a new definition with a conceptual framework, bringing preterm birth, SGA, and LBW together under a broader umbrella term - the "small vulnerable newborn" (SVN).

4. Interventions that focus on the health of women and fetuses, can reduce newborn vulnerability, stillbirth, and maternal ill-health, leading to thriving individuals, families and nations.

Summary

Despite major achievements in child survival, the burden of neonatal mortality has remained high and even increased in some countries. Currently, most neonatal deaths are attributable to being born preterm, small for gestational age (SGA), or with low birth weight (LBW). Besides neonatal mortality, these conditions are associated with stillbirth and multiple morbidities with short- and long-term adverse consequences, in the newborn, their families, and society at-large, resulting in a major loss of human capital. Prevention of preterm birth, SGA, and LBW is thus critical for global child health and broader societal development. Progress has, however, been slow, largely because of the global community's failure to agree on the definition and magnitude of newborn vulnerability and best ways to address it, to frame the problem attractively, and to build a broad coalition of actors and a suitable governance structure to implement a change. We propose a new definition and a conceptual framework, bringing preterm birth, SGA, and LBW together under a broader umbrella term of the "small vulnerable newborn" (SVN). Adoption of the framework and the unified definition can facilitate improved problem definition and better programming for SVN prevention. Interventions aiming at SVN prevention would result in a healthier start for live-born infants, whilst also reducing the number of stillbirths, improving maternal health, and contributing to a positive economic and social development in the society.

The importance of newborn vulnerability

Child health and wellbeing have been a global development priority for decades. Improved child survival was one of the United Nations eight Millennium Development Goals[1], remains an important target in the United Nations Sustainable Development Agenda[2], and is emphasised in many global initiatives such as the United Nations Global Strategy for Women's, Children's and Adolescent's Health. [3] During the period of increased global attention, child survival has improved remarkably.[4] Between 1990 and 2021, the number of deaths of children under 5-years of age worldwide fell by 61%, from 12.8 to 5.0 million per year.[5]

The positive trend in child survival has been documented in all age-groups, but unfortunately not quite evenly; mortality in the neonatal period (in the first 28 days of life) has declined more slowly than that among older children.[6] As a result, neonatal mortality now accounts for almost half of all under-5 mortality in the world.[5] Strikingly, there are countries and regions that in absolute terms experienced even more neonatal deaths in 2021 than in 1990. Neonatal mortality rates (expressed per 1000 live births) have also decreased in these settings, but these reductions have been offset by larger increases in the numbers of births (**Supplemental table 1**).[5,7] This early mortality is seen as a major hindrance to development especially in Sub-Saharan Africa, where health is becoming a priority for future nation building.[8]

Globally, and especially for low and middle income countries (LMICs), most authorities list preterm birth, intrapartum complications (birth asphyxia and birth trauma), and infections as the main direct causes of neonatal deaths.[9] Preterm birth is considered the cause of death when it is associated with respiratory distress syndrome, intracranial haemorrhage or other complications of fetal immaturity.[10] In addition to the directly attributed deaths, preterm birth increases the risk of death due to infections.[11] In many settings, where gestational age at birth is uncertain, low birth weight (LBW) is listed instead of preterm birth as a major cause of neonatal mortality.[12] Although rarely considered a direct cause, newborns who are smaller than expected for their gestational age (SGA) also have an increased mortality risk.[13] In most cases being born SGA indicates that the infant has experienced harmful intrauterine exposures resulting in fetal growth restriction. In a small minority of individuals, it can indicate constitutional smallness. Together, preterm birth, LBW, and SGA account for most of the early mortality. It has been estimated that as many as 80% of all neonatal deaths in the world occur in LBW infants, of whom two-thirds are likely preterm and one-third SGA.[14]

There are no unified databases on the overlap between different newborn types, but approximately 10% of the world's infants are born preterm and the proportions of newborns with LBW or SGA are estimated to be even higher.[14–16] Besides mortality[13,17], these newborns have an increased risk for undernutrition[18], metabolic disorders[19,20], developmental delay[21], and a multitude of adverse health conditions throughout their lifespan.[22] Prevention of preterm birth and small birth size is therefore critical for global health and well-being and forms the basis for this *Lancet* series. Its article collection builds on and supplements the WHO-UNICEF-Lancet Commission on Child Health[23], the Optimising Child and Adolescent Health and Development series[24], and several other earlier *Lancet* series on maternal and child health.

In the first article of the series, we will review the evolution of constructs for identifying preterm or small newborns. We will demonstrate a considerable overlap in preterm birth, SGA, and LBW, in terms of their determinants and implications for health and survival outcomes. For public health purposes, we propose to merge them under a new holistic term of "small vulnerable newborn" (SVN), recognizing, however, that there are differences in clinical management of the different SVN types, applicable especially in high-resource settings. Finally, we will identify challenges that will need to be overcome and myths that need to be broken for successful SVN prevention.

To provide a comprehensive description of the magnitude of the SVN problem and to provide the rationale for preventive interventions, the second article in the series will provide novel estimates on SVN prevalence and risks based on large, individually linked datasets[25]. The subsequent two articles will describe the biological basis and expected benefits from preventive interventions, by reviewing pathophysiological mechanisms leading to SVN births[26] and outlining evidence-based interventions within the antenatal care package and estimating their potential impact on health and well-being.[27] In an associated comment, there will be a call for action for promoting women's, maternal and fetal health, minimising newborn vulnerability, and supporting a healthy start for every newborn.[28]

Since there is an urgent implementation gap for SVN prevention, the included articles focus on that and will not discuss prevention of other newborn vulnerabilities, such as hypoxic injury, perinatal infections, or being post-term or term and large for gestational age. These issues as well as the management of the sick and vulnerable newborns are planned to be discussed in detail in another series in *the Lancet*. We will also not discuss strategies which would reduce but are not specific to SVN, such as enhanced contraception services.

Evolution of criteria for identifying high-risk newborns: From LBW to SVN

Currently, there are three main constructs used to define small newborns who have an increased risk of adverse health outcomes: LBW, preterm birth, and SGA. These definitions have evolved over the past 100 years, as a function of advancing knowledge and technology, and changing evidence and diagnostic priorities among health professionals **(Box 1)**. All three definitions are being used, but for varying purposes and by different professions. LBW has traditionally been used worldwide in clinical practice, epidemiological research, and in public health comparisons, such as United Nations statistics. The definition of preterm birth is of special interest to obstetricians and midwives who make decisions about the management of individual pregnancies based on the risk of early delivery. Additionally, it is used by paediatricians and neonatologists making care-related decisions based on the estimated "maturity" of the newborn. SGA is utilised by neonatal and paediatric practitioners and researchers, especially in the field of nutrition, and its antenatal correlate fetal growth restriction is used by obstetricians and midwives for antenatal decision-making.

The use of three different dichotomous definitions for newborns who are preterm or small in absolute or relative terms is understandable, given the historical evolution of the terms and fragmentation of the communities who use the data. However, there are also major disadvantages to this practice. First, the definitions convey different types of information: preterm birth and SGA indicate processes that lead to newborn vulnerability, whereas LBW indicates only small birth size, with no reference to its determinants. Importantly, the use of multiple definitions makes it difficult to determine the total burden of the small newborn problem, since each definition is incomplete. In a recent dataset including over 18 million births from Brazil between 2011 and 2018, the prevalence of preterm birth was 9.4%, SGA 9.2%, and LBW 9.6%. However, 18.0% of the newborns were included in at least one of the categories, indicating that the use of any one of the individual definitions would underestimate the number of all at-risk newborns by approximately 50%.[29]

In addition to providing an incomplete estimate, the use of several different criteria obscures that the same newborn can belong to more than one group. When combined, the LBW, preterm, and SGA cut-offs define a total of seven possible newborn types, of which six indicate a special vulnerability and only one is "non-risk".[30] For simplicity, and based on mortality risk analyses[25], vulnerable newborns can be categorised into three main groups: preterm newborns, those who are SGA (most of whom were subject to fetal growth restriction), and those who are both preterm and SGA. Of these, the preterm-SGA newborns have the highest risk of neonatal death, followed by preterm but not SGA infants.[13,29] An analogous risk gradient has been shown for post-neonatal infant mortality[29,31] and child mortality[29] and may also apply to other adverse health sequelae.

Although the exact mechanisms leading to preterm birth, SGA, and LBW and the clinical management of the affected newborns are different[26] they share many risk factors, aetiologies and consequences. All these newborns are also "small" in some respect: either in the duration of their fetal life (preterm infant), absolute size (LBW), or size relative to the duration of pregnancy (SGA). For public health purposes, we therefore propose a new unifying concept of "Small Vulnerable Newborn" (SVN), encompassing all newborns who are preterm or SGA, or have LBW (**Box 2**). Because of its inclusiveness, adopting this concept will improve estimates of the global burden and facilitate better public health programming and monitoring of progress.

Conceptual framework of SVN: Multiple causes, three types, wide adverse consequences

Our conceptual framework is structured similarly to the one WHO used for childhood stunting.[32] It assumes that there are contextual factors (root causes) that predispose mothers and fetuses to adverse exposures (immediate causes), leading to fetal growth restriction, preterm birth, or both. These two mechanistic pathways can result in three main SVN types. Under very adverse conditions, the same pathways can lead to fetal death, i.e., a miscarriage or stillbirth. For the liveborn SVN, mother, family, and wider society, there are multiple short and long-term adverse consequences (**Figure 2**).

The contextual factors include broad social determinants of health, such as poverty[33], armed conflict[34], and political instability.[35] High food prices[36,37] and poor food security[36,38,39] make women susceptible to undernutrition and problems with water, sanitation and hygiene also to infections.[40] Environmental pollution and climate change can reduce newborn size through multiple mechanisms, including undernutrition and physiological changes in the mother, or trans-placental exposure of the fetus to harmful environmental compounds.[41] Poor maternal education may reduce maternal socioeconomic status and access to antenatal care and other health services[42–46] and problems in health systems governance will further limit the availability and quality of services.[47] Finally, cultural beliefs, norms and social support given to a pregnant woman may affect her dietary patterns, macro- and micronutrient intakes, smoking, other health-related behaviours and health care utilisation, ultimately also affecting the duration of pregnancy and newborn size.[48–50]

The most commonly highlighted adverse exposures that initiate or contribute to fetal growth restriction and preterm birth include maternal underweight[51], short stature[52], anaemia[53–55], and infections.[56–60] Another large group includes various environmental exposures, such as air pollution[61–63], intimate partner violence[64,65], physical workload[66], and tobacco[67] or alcohol[68,69] consumption. In total, these three clusters of potentially modifiable risk factors, i.e., maternal nutrition, infections, and environmental exposures, are estimated to account for approximately 50% of spontaneous preterm birth[70] and 39% of SGA in LMICs.[70,71] The relative importance of the risk factors varies by region, infections being associated with the largest fraction of SVN in Sub-Saharan Africa and nutrition being most important in Southern Asia.[70,71]

In addition to these three large risk factor clusters, there are also several other modifiable risk factors, such as maternal depression[72], stress[73], gestational diabetes[74], endometriosis[75], short uterine cervix[76], high or low age maternal age[77,78], high or low parity[79] and short interpregnancy interval.[80,81] Finally, there are risk factors that do not fit into any of the previously mentioned groups, such as multiple pregnancy[82] and residence at high altitude.[83] Most of the stated risk factors have been associated both with fetal growth restriction and preterm birth, some with only one of the pathways.

For a landscape analysis on adverse outcomes associated with preterm birth, SGA and LBW, we conducted a scoping review of English language literature, searching for systematic reviews, meta-analyses, and other research syntheses in Ovid Medline, CINAHL and Embase databases. The results confirmed that SVN types are associated with increased neonatal morbidity and mortality[84,85,86,87,88,89,90,91,92,93], and also with child undernutrition, neurodevelopmental impairment, behavioural problems, and excess morbidity and mortality in adolescence and adult life (**Table 1**). Importantly, there are also many adverse social and economic consequences to the newborn's family, such as increased risk of parental stress[94], poor parental sleep quality [95,96], and reduced likelihood of the parents having additional children.[97] For society, there is increased expenditure on health care[98, 99] and loss of human capital, due to excess mortality and lower educational attainment.[100] Many of the studies have used a dichotomised outcome variable (preterm birth, LBW, or SGA), but others have shown that the risk for an adverse outcome rises progressively with extremes of preterm and SGA.

Slow progress in SVN prevention despite increasing global attention on newborn health – why?

So far, there have been few global statistics on trends in SVN prevalence, mostly because of missing or non-standardised data collection on SGA births. However, LBW prevalence trend serves also as a good proxy for all SVN births. **Figure 3** shows the latest United Nations estimates for LBW births in 195 World Health Organization members states from 2000 to 2020.[101] At present, approximately 20 million infants are born with LBW each year, with little decline overall in the past 20 years. In absolute numbers, there has been a small reduction in Southern Asia and an increase in Sub-Saharan Africa – but these changes reflect mostly trends in the numbers of livebirths, rather than changes in LBW prevalence.

The lack of progress in LBW and SVN prevention can be considered surprising, given the plethora of related high-level attention and targets (**Box 3**). To understand this apparent contradiction, we used a published framework that outlines four main challenges which global health networks face in generating attention and resources for the conditions they are concerned about.[102] By networks we refer to webs of individuals and organisations linked by a shared concern for their issue. The four challenges, identified in a research program that examined eight networks engaged in public health, include problem definition, positioning, coalition-building, and governance.[102] According to our subjective analysis, inadequate response of the global community to each of these four challenges has contributed to the persistence of the high SVN prevalence (**Table 2**).

With respect to "problem definition" on SVN prevention, the use of three different definitions (preterm birth, SGA, and LBW) for newborn vulnerability has impeded estimation and appreciation of the full burden and fragmented the clarity on interventions and tractability of prevention. Additionally, although WHO has recently published several recommendations for improving pregnancy outcomes both for the mother and newborn[103–107], there is no internationally agreed document that would concomitantly cover all SVN types and specifically address prevention. The ENAP identified delivery and postnatal care and management of small and sick newborn as priority package for improving newborn health, with antenatal care as key for prevention of stillbirths. Whilst the importance of preventive interventions was discussed in the background articles, there was less evidence for interventions with high and immediate impact.[108] Because of the confusion on the definition, emphasis on care, and the widespread ambiguity regarding how to address prevention, it has been difficult to mount collective intervention. Therefore, we rate response to the "problem definition" challenge as "contested", i.e., inadequate.

With respect to "positioning" SVN prevention, we also rate this response so far as "contested" (inadequate), as the issue has usually been framed as a purely medical problem. This approach is obvious, but too narrow according to many stakeholders. Other metaphors that global health networks have used for justifying investments include improvement of public health, an act of charity, a fulfilment of human rights or social justice, a tool for foreign policy, an investment into social and economic development, a resolution to a humanitarian crisis, and a safeguard of security.[102,109,110] Of these alternative framings, at least public health, human rights improvement, and investment into societal development fit well to SVN prevention, given the mortality, morbidity and human capital loss associated with being born too soon or too small.

For "coalition-building" we rate the current response as "moderately broad". A joint WHO/UNICEF steering committee, including national government representation, is actively coordinating the ENAP. The original plan was passed as a resolution at the 67th WHA and there will be periodic progress reports until 2030.[111] The countries have also set a new round of targets in 2020-2025 and defined antenatal care as a priority. There are also several large networks of relevance, notably the Partnership for Maternal, Newborn and Child Health

(PMNCH), which operates at head of state level and with inter-sectoral linkage. The Inter-Agency Working Group on Reproductive Health in Crises (IAWG) is especially key for the many countries affected by humanitarian emergencies, and there are also other, smaller networks. However, none of the coalitions focuses solely or predominantly on SVN prevention. Like many other global health networks, they are also mostly technically focused and insular, enlisting like-minded actors in the health sector, but missing broader political alliances such as grassroots civil society actors, heads of government, parliamentarians, and ministers of finance, nor do they involve representatives of affected families – the vulnerable newborns and their parents. Without these stakeholders, major progress will be difficult.

For the fourth challenge, "governance", we rate the current response as "largely cohesive". Both ENAP, PMNCH, and IAWG have clear organisational structures and they do address SVN issues. However, the stakeholders do not have a clear unified structure for collaboration especially on SVN prevention. There are at least three alternatives for this function: a shared network where members interact on a relatively equal basis (a model used by ENAP), a lead organisation-based system where activities are mostly coordinated through a single member, and an administrative model, where a separate entity is set up specifically to govern the network's activities (a model used by PMNCH).[112] Each network is different and needs to make its own decision about the collaborative model. The fact that there are several models for SVN prevention, makes it difficult to agree on a coordinated target, action plan, quality assurance, monitoring framework, or indicators of success.

Management is silver, prevention is gold

The main stakeholders in SVN prevention are women of preconceptional age and dyads that consist of a pregnant woman and her baby. The woman's vulnerabilities need to be addressed primarily because of their possible adverse impact on her own health. But the woman's vulnerabilities are also carried to her offspring, increasing the risk to be born too soon or too small and suffer from multiple negative consequences throughout the lifespan. Also important, is that the same adverse exposures that result in fetal growth restriction or preterm birth, also contribute to some of the 23 million miscarriages, two million fetal deaths (stillbirths), approximately 350,000 maternal deaths, and a significant amount of maternal morbidity that happen each year.[113–115] Thus, there is a vicious cycle from vulnerable girls and women to vulnerable newborns, continuing to vulnerable adults, families, and societies. Interventions that focus on the health of women and fetuses, can break this cycle and push the balance to thriving individuals, families and nations (**Figure 4).**

Some of the interventions that are necessary for ensuring good pregnancy outcomes can be offered during antenatal care. However, for a maximal impact, it will be critical to address also the social determinants that can negatively impact pregnant women's health and health seeking behaviour. These include the root causes shown in Figure 2, such as poverty, unsafe living environment, lack of education and agency, and the accessibility and quality of antenatal care and other health services that the woman is receiving.

Interventions and policies for maternal and fetal health promotion and SVN prevention will be discussed further in articles 4 and 5 of this series.[27,28] For a successful outcome, it will also be important to tackle two apparent myths that have hampered progress and replace them with views that are based on recent scientific evidence. The first of these is a belief, that the small birth size problem is unpreventable in low-income settings. This misconception probably stems from the fact that most evidence on possible positive effect on prevention comes from single-intervention trials.[116] The limited effect in trials with such a narrow focus is not surprising, given the complexity of the aetiological network: a single-pronged intervention is unlikely to solve a multifactorial problem. For instance, if undernourished children have concomitant infections, they may lack the ability to respond to dietary supplements.[117] However, if one uses a package of interventions that addresses maternal health, nutrition, and social wellbeing through multiple platforms, both before and during pregnancy, as occurred in the recent WINGS trial in India, the prevalence of LBW can be markedly reduced in just one generation.[118]

The second myth is that it is impossible to produce accurate statistics on SVN since birth weight and gestational age are often measured inaccurately. Ultrasound-based estimation of gestational age is also often seen as expensive, complicated to use, and unreliable for the many women who start antenatal care late. These challenges are real but surmountable. The quality of birth weight data can be improved by increasing the proportion of facility births and providing standardised scales, as well as better training on their use and how to record birth weights[119] and calculate weight for gestational age. Ultrasound technology is becoming less expensive, low-cost devices are easier to use,[120] and women are enrolling in antenatal care much earlier than before, especially in LMICs.[121,122] Moreover, algorithms now exist that allow gestational age to be determined later in pregnancy.[123,124] Further standardization on the gestational age assessment method will be necessary, but already now it is feasible to date all pregnancies reliably also in LMICs, as recommended by WHO. [125,126]

Rapid progress in child survival proves that change is possible with global commitment and local determination and action. Placing more focus on SVN prevention will complement the earlier child health activities and facilitate achievement of the United Nations Sustainable Development Goal 3.2 that calls for neonatal mortality reduction.[2] Importantly, such a focus will likely provide many additional short- and long-term health benefits both to the mother and the newborn and for stillbirth prevention, translating into increased human capital and a positive development spiral. The time to act is now. Every newborn, family, and society has the right to survive and thrive.

Contributors

PA, UA, SA, REB, JH, NK, JEL, and MT designed the study and planned the data analyses. PA, YM, and UA had access and verified the underlying data and PA conducted the analyses. All authors participated in the conceptualisation and drafting of the original manuscript, reviewed and edited subsequent drafts, and approved the final version of the manuscript. PA made the final decision to submit the manuscript.

Declarations of interest

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Box 1. Evolution of criteria for identifying high-risk newborns

LBW was the first definition to be formalised for a small, at-risk newborn. The currently used cut-off of 2500 g was initially published approximately 100 years ago by Dr. Arvo Ylppö, a Finnish paediatrician working in Germany.[127] The 2500 g cut-off did not have a biological justification, and it seems to have been selected as a round figure that encompassed approximately 5% of newborns. This assumption is supported by the fact that authors in the United States suggested another round cut-off using the imperial measurement system (5 lb., i.e., 2270 g).[128] The American Academy of Pediatrics, other professional organisations and the World Health Organization (WHO) codified the 2500 g cut-off as an indication of “prematurity” between 1935 and 1948.[129,130] A 1961 report by a WHO Expert Committee on Maternal and Child Health highlighted the difference between preterm infants and term but small infants and suggested changing the term from “premature babies” to “babies with low birth weight”.[131]

Although the first criterion for a small newborn was birth weight, the definition itself seemed to refer more to a short pregnancy duration. The German-language term that Dr. Ylppö used for small infants was “frühgeborenen”, meaning “early born” and the term used in respective US studies was “premature”. In the 1948 International Classification of Diseases (ICD), in which WHO adopted the 2500 g cut-off, the condition was called “immaturity”. Interestingly, the text noted that “*if birth weight is not available, a liveborn infant with a period of gestation of less than 37 weeks or specified as "premature" may be considered as the equivalent of an immature infant*.[130] With the development and spread of obstetric ultrasound technology there was increasing interest in a more specific definition for a birth that occurred early. In 1970 a working group of obstetricians and paediatricians at the Second European Congress of

Perinatal Medicine set the boundary between "preterm" and "term" birth at 37 completed weeks of gestation.[132]

As with LBW, there was no justification given to the cut-off selected for preterm birth. Alternative possibilities were apparently discussed, but eventually 37 weeks was chosen because it had already appeared in the 1948 ICD. The 37-week cut-off and the expression "preterm birth" were officially adopted by WHO in its International Classification of Diseases in 1977.[133] Several authors and organisations have subsequently suggested a later cut-off of 39 weeks' gestation, because it would better coincide with functional maturity.[134] So far, 37 weeks' gestation has persisted as the most widely accepted cut-off for preterm birth. However, to account for the stated concerns and to allow a more stratified risk assessment, the American College of Obstetricians and Gynecologists recommends term deliveries to be sub-classified into early term (37.0 - 38.9 weeks), full-term (39.0 – 40.9 weeks), late term (41.0 – 41.9 weeks), and post term (42.0 weeks or more) categories.[135]

The third category used for small newborns stemmed from the concern of health professionals having to define small but term infants "premature" as suggested by the 1948 ICD. Several publications in the 1950s and 1960s highlighted the fact that, in addition to preterm birth, LBW results from what was originally called "intrauterine growth retardation".[136–139] The process of impaired fetal growth has since been renamed fetal growth restriction, and infants who are born with a birth weight that is below an agreed cut-off for their sex and gestational age as SGA.

A WHO Expert Committee adopted the concept of SGA and recommended the use of a US-based, multiracial "Williams" reference in 1995.[140] This was soon replaced by another US-based "Alexander" reference, that classified newborns below its 10th centile as SGA.[141] In 2007, the International Society of Pediatric Endocrinology and the Growth Hormone

Research Society suggested that a cut-off of -2 standard deviations from the mean would be more appropriate than the 10th centile, as it would identify only 2.3% and not 10% of newborns as SGA.[142] Between 2014-2016, the INTERGROWTH-21st Consortium published new sex and gestational age specific birth size standards for term, preterm and very preterm newborns, based on the same prescriptive approach that produced the WHO Child Growth Standards.[143] Because of its multinational cohort, the INTERGROWTH-21st standards were designed to have better global validity than a purely US-based reference.[144145] Many recently published scientific manuscripts use the INTERGROWTH-21st birth weight standard and a cut-off below the 10th centile to define SGA, but there is no official consensus on its use and the discussion about the correct reference and cut-off to use continues.[146–148]

Figure 1 summarises the key milestones in the development of the small newborn definitions. For all these definitions, there is a corollary indicative of a large birth size or long duration of pregnancy, i.e., high birth weight, post-term birth, and large for gestational age. Whilst these states also confer an increased health risk for the newborn, their global health impact has been less studied, and they will not be covered in the current *Lancet* series.

Box 2. Definition of a Small Vulnerable Newborn

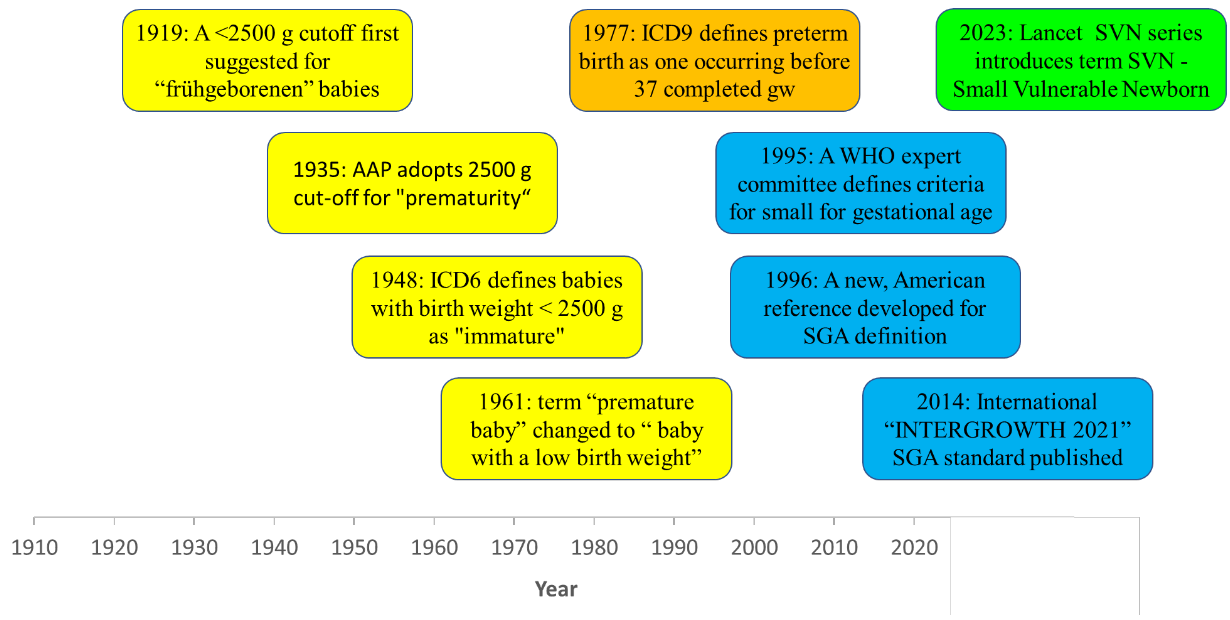
Our definition of Small Vulnerable Newborn includes all live newborns who are preterm (born before 37 completed weeks of gestation), are small for gestational age at birth (birthweight below the 10th centile of the recommended international, sex-specific birthweight for gestational age standard) or have low birth weight (<2500g).

In principle the definition could be based only on preterm and SGA, encompassing practically the full set of small newborns who have an increased risk of mortality and other adverse outcomes.[25] Preterm and SGA represent the driving pathways for vulnerability, i.e., duration of pregnancy and fetal growth restriction, and therefore guide the prioritization of preventive interventions and clinical management, whereas LBW does not give this important information. Therefore, we focus on preterm, SGA, and preterm-SGA that are the causes of LBW and are associated with increased risk of mortality and other vulnerabilities both in newborns who do or do not have LBW. However, birth weight is still more commonly measured than pregnancy duration or SGA and easily understood by parents. As opposed to SGA and preterm birth, there is also a global target for reducing LBW prevalence.[149,150] Hence having LBW in the definition will facilitate continuation of monitoring of current targets and identification of vulnerable newborns even in contexts where antenatal services are most limited. In the future, once pregnancy dating and SGA monitoring have become the norm worldwide, the inclusion of LBW in the SVN definition may become less important.

Box 3. Examples of high-level attention to LBW and SVN prevention, 1990 - 2020

The reduction of LBW prevalence to less than 10% was defined as a key nutritional goal already in the 1990 World Summit for Children.[151] In 2012, WHO, supported by many other organisations, published a "*Born Too Soon*" report that had high political resonance and lots of attention, calling for primary prevention of preterm births and better care for preterm infants.[152] Soon afterwards, the World Health Assembly (WHA) set the reduction of LBW prevalence by 30% between 2010 and 2025 (later extended to 2030) as a global nutrition target[149,150] and an article series on maternal and child nutrition in *The Lancet* called attention to the large number of neonatal deaths attributable to SGA.[153] In 2014, the *Every Newborn* series in *The Lancet* led to the WHO and UNICEF facilitated "*Every Newborn Action Plan*" (ENAP), with a World Health Assembly Resolution and the first Sustainable Development Goal (SDG) target for newborn survival.[111] Both the *Born Too Soon* report and the ENAP underlined the impact of small birth size on mortality and disability, calling for emphasis and investments in small and sick newborn care but also for primary prevention through the maternal and child life course.[154–156] The publication of ENAP led to an ongoing active partnership of more than 100 organisations, co-chaired by WHO and UNICEF. As part of this process, more than 90 countries have set specific targets for newborn survival and are regularly reporting on progress.

Figure 1. Key milestones in the evolution of vulnerable newborn terminology. Yellow boxes denote the development of the low birth definition, orange box marks the adoption of the preterm birth definition, blue boxes refer to the definition of small for gestational age and the green box refers to an umbrella term combining the former three definitions. Frühgeborenen born early, AAP American Academy of Pediatrics, ICD International Classification of Diseases, adopted by the World Health Assembly, WHO the World Health Organization, gw gestation weeks, SGA small for gestational age



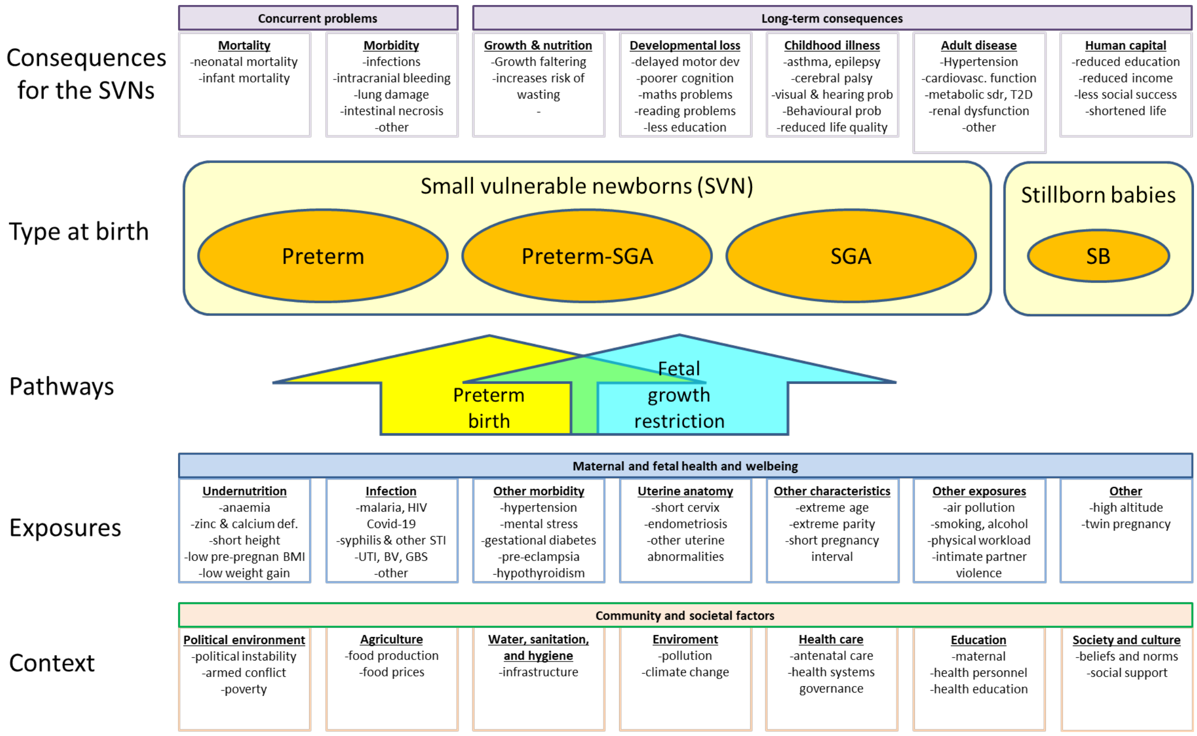


Figure 2. Conceptual framework for the causes and consequences of being born small. Dev development, prob problems, Sdr. syndrome, T2D type 2 diabetes, SGA small for gestational age, SB stillbirth, BMI body mass index, HIV human immunodeficiency virus infection, STI sexually transmitted infections, UTI urinary tract infection, BV bacterial vaginosis, GBS group B streptococcus

Figure 3. Annual numbers of newborns with LBW between 2000 and 2020, by region. Estimates by UNICEF and WHO for 195 countries from 2000 to 2020. National annual LBW rates with smoothing applied to national live births per year, as described earlier.[101] LBW low birth weight

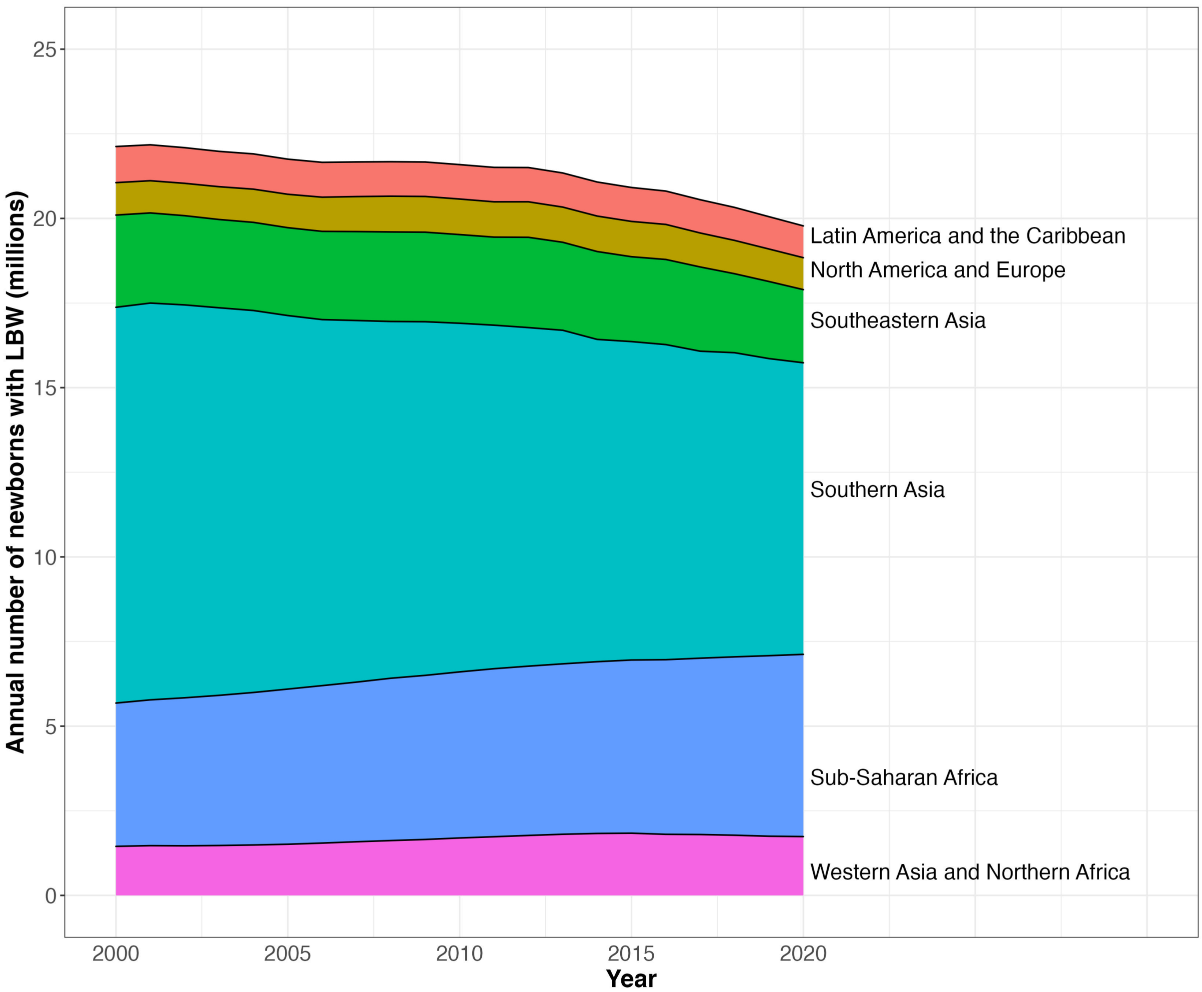


Figure 4. The vicious cycle between vulnerable newborns and vulnerable societies

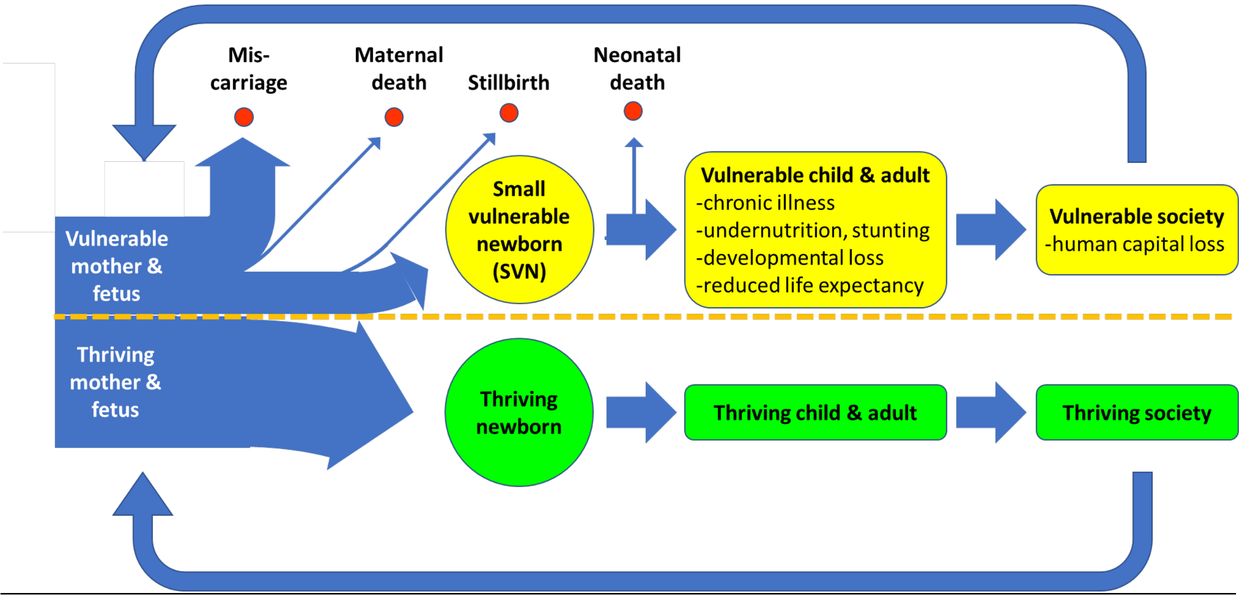


Table 1. Adverse outcomes associated with SVN in systematic reviews and meta-analyses

Childhood

Increased risk of mortality, stunting, and wasting (PT, SGA)[13,18]

Increased risk of cerebral palsy and epilepsy (PT) [157,158]

Reduced brain volume (PT, LBW)[159]

Increased risk of wheezing disorders and asthma (PT, LBW)[160,161,162,163,164,165,166]

Reduced lung function and exercise capacity (PT, SGA) [161,167,168]

Morphological and functional cardiac impairments (PT)[169]

Increased risk of hepatoblastoma and acute myeloid leukemia (PT)[170],[171]

Hip bone shape abnormalities and increased risk of hip osteoarthritis (PT, LBW)[172]

Altered palatal morphology and defects in dental enamel (PT, LBW)[173,174,175]

Increased risk of delay and impairment of neurodevelopment (PT, SGA)[176,177, 21,178]

Problems in motor development (PT, LBW)[179,180 ,181 ,182,183,184,185,186187]

Reduced IQ and cognitive performance (PT, SGA, LBW)[188,179,189,190,191,192,193,194,195,196,180,197]

Blindness and other problems with vision (PT, SGA)[198,199,200,201,202]

Problems in reading, spelling, and mathematics (PT)[179, 189,203]

Reduced language abilities and increased risk of dysphonia (PT, LBW)[204,205,206,207]

Impaired school and academic performance (PT, LBW)[157,179,181,192,196, 208, 209, 210 ,211]

Increased risk of ADHD and autism spectrum disorders (PT, LBW,SGA)[193,212,213,214,215]

Increased risk of mental disorders & social problems (PT, LBW)[216,217,181,213,212,218]

Reduced self-rated quality of life (LBW, PT)[219]

Adolescence

Increased risk of asthma and poor lung function (LBW, PT) [164,166,167, 168]

Cardiac and vascular problems and increased blood pressure (PT, LBW)[169,220,221]

Reduced IQ and cognitive performance (LBW, PT) [179,222]

Increased risk of depression, anxiety, and being bullied (SGA, PT, LBW)[223,224,225226]

Increased frequency of school problems (PT)[227]

Increased risk of social difficulties and behavior problems (LBW, PT) [179,213]

Increased risk of a psychiatric diagnosis and hospitalization (PT)[224,228]

Reduced sleep quality and increased risk of sleep breathing disorders (PT) [229,230]

Reduced self-rated quality of life (LBW, PT)[219,231]

Adulthood

Increased morbidity and mortality (PT)[232,233]

Reduced lung function and increased risk of asthma (LBW)[165,234]

Impaired renal function (LBW, PT)[235,236,237,238]

Increased risk of metabolic syndrome and diabetes (LBW, PT)[239,240,20,241,242,243,241,244]

Increased risk of hypertension, coronary disease and stroke (PT, LBW)[221,239,244 ,245,246,247,248]

Increased risk of testicular cancer (LBW)[249]

Increased risk of hip arthroplasty for osteoarthritis (PT)[172]

Increased risk of depression and anxiety (SGA, PT, LBW) [213,223,250]

Increased risk of shyness, social withdrawal, autism, and physical inactivity (PT)[213,228,251 252]

Increased use of psychotropic medication (PT, LBW)[253]

Decreased likelihood of completing higher education and being employed (PT, LBW)[254]

Decreased likelihood of a romantic partnership and becoming a parent (PT, LBW)[255]

Reduced quality of life (PT)[231]

SVN small vulnerable newborn, PT Preterm birth, LBW Low birth weight, SGA Small for gestational age, ADHD Attention deficit and hyperactivity disorder

Table 2. Success of global response to main challenges in SVN prevention.

Challenge	**Meaning**	**Status for SVN prevention**	**Description**
Problem definition	Generating evidence-informed consensus within the global health network on the definition of, and best ways to address the problem	Contested[1]	The three different definitions for adverse birth outcomes compete with each other and complicate a comprehensive synthesis of the problem. Improved management, but not prevention, is seen as a priority.
Positioning	Framing the issue in a way that moves key actors external to the network to provide resources.	Contested	Preterm birth, SGA, LBW typically positioned individually and only as a medical problem for the newborn. Maternal ill health, miscarriages, and stillborn babies are ignored and the life-long impact of SVN and loss of human capital are largely ignored.
Coalition-building	Recruitment of allies beyond core members of the global health network.	Moderately broad	Every Newborn Action Plan pulled together many partners and lead to the formation of multiple international networks. But they involve mainly organisations from the health and health research sector. National governments and actors are underrepresented, and SVN and their parents have no voice.
Governance	Establishing institutions to facilitate collective action	Largely cohesive	No apparent central guiding forum or institution that brings together primary organisations. Only LBW tracked and with a global target.

[1]Possible categories for "Problem definition and preferred solution" and for "Positioning" include cohesive, relatively cohesive, and contested. Possible categories for "Coalition building" include broad, moderately broad, and narrow and those for "Governance" include cohesive, largely cohesive, and fragmented. Framework adopted from Shiffman[102]. SGA small for gestational age, LBW low birth weight, SVN small vulnerable newborn

Supplemental table 1. Number of births and neonatal deaths in different world regions, 1990 and 2021

World Region	Annual number of births (thousands)			Neonatal mortality rate (deaths per 1,000 live births)			Neonatal deaths (number of deaths) thousands		
	1990	2021	Decline (percent)	1990	2021	Decline (percent)	1990	2021	Decline (percent)
Sub-Saharan Africa	22,086	39,441	-79[1]	46	27	41	1,004	1,067	-6
Northern Africa	4,673	5,928	-27	34	15	54	157	91	42
Southern Asia	39,910	36,086	10	57	22	61	2,288	811	65
Eastern Asia	31,039	12,640	59	28	3	89	853	39	95
South-Eastern Asia	11,963	11,086	7	28	12	58	332	130	61
Western Asia	4,824	5,643	-17	28	11	58	133	65	51
Central Asia	1,594	1,772	-11	28	10	66	44	17	62
Europe	9,235	6,880	26	8	2	70	76	17	78
North America	4,568	4,098	10	6	3	42	26	13	48
Latin America & the Caribbean	12,020	9,709	19	23	9	60	272	87	68
Oceania	540	693	-28	13	10	48	7	7	0
World	142,451	133,975	6	37	15	52	5,191	2,345	55

[1]All percentages calculated from unrounded numbers. Birth data source: World Population Prospects: The 2022 Revision -United Nations Population Division.[7] Neonatal death and mortality data estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation.[5]