The Golden 28 days of child survival

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ABSTRACT

Background: The first month of life is undeniably the most vulnerable period for the child's survival. Despite child mortality has decreased by 56% from 1990 to 2015, the 2/3rds reduction stipulated by Millennium Development Goals (MDGs) 4 has not been achieved.

Main text: Whereas annual decrease of children aged 1-59 months has been 4.7% its equivalent in neonatal mortality (NM) was 3.1%. The targeted MDG 4 would have been possible if neonatal deaths had been declining at a rate achieved by the 1-59 month age group. NM has become an increasing driver of the overall global paediatric mortality, representing an increasing proportion of all annual child deaths. Thus, almost half of children under five die in the first month of life, and most of them, in the first week. The new Sustainable development goals (SDGs) specify an even more ambitious global target by 2030. In order to achieve this target, international community have to tackle main cause of deaths (CoD) among neonates, otherwise, the world will fail to significantly reduce overall child mortality. To improve evidence-based data on CoD is essential to know why children are dying. Innovative techniques such as the post-mortem minimally invasive tissue sampling may provide reliable data and thus contribute to better characterize mortality in this age group. Universal coverage of essential interventions tackling main CoD among neonates has the potential to reduce neonatal deaths by an estimated 71%, benefit women and children after the first month, and reduce stillbirths.

Conclusion: The SDG target aims to reduce neonatal deaths to a maximum of 12 per 1000 live births in every country of the world by 2030. If every country achieves this target, approximately 5 million neonatal lives will be saved throughout the period 2017-2030 and all of the efforts focused in helping neonates go through "the golden first 28 days of life" will have been worthwile.

KEYWORDS: neonatal mortality, neonatal deaths, child mortality, cause of death, sustainable development goals.

BACKGROUND

The first two decades of the 21st century can indisputably be characterized by a global health revolution that has led to massive improvements in health outcomes, particularly in terms of child survival. Indeed, never before in the history of mankind the chances of surviving for any new baby born in this world have been greater, with child mortality becoming anecdotal in many industrialized regions, and the number of child deaths decreasing globally at a fast pace, from over 17 million annual deaths in the 1970's to around 5.6 million in 2016[1,2]. Such unprecedented and impressive reductions are the result of many national and international efforts and coinciding circumstances, but have essentially been catalyzed by the establishment, back in the year 2000, of the Millennium Development Goals (MDG), a set of laudable aims agreed upon by all 191 United Nations countries, designed to combat poverty, hunger, disease, illiteracy, environmental degradation, and discrimination against women[3]. Many countries succeeded in achieving in the period 1990-2015 the 2/3rds reduction in child mortality stipulated by MDG4, but global progress was unequal, and the global target has not been completely achieved[4]. The particular push and drive for child survival provided by the MDGs has now been taken over by the more recent Sustainable Development Goals (SDGs), and in particular by SDG3.2[5], which specifies an even more ambitious global target, to be achieved by the year 2030, and which should be seen as a new opportunity to save millions of lives.

MAIN TEXT

Such applauded decreases in child mortality achieved in the last decades offer significant nuances. From a geographical and socio-economic point of view, and despite the fact that such falls have been confirmed in all areas of the world, reductions have been more modest in low- or middle- income countries (LMIC) and in particular in Sub-Saharan Africa (SSA). It is no coincidence that up to 99% of all child deaths are now circumscribed to these settings[6,7], a strident reminder of the many inequities driving global health. From an age category point of view, neonatal deaths, those defined as occurring within the first 28 days of life, have also decreased, but at a much slower rate, estimated at around 3.1% annually, from the 30 deaths per 1000 live births in 2000 to 19 in 2016[1,2,8]. Thus, neonatal mortality has become an increasing driver of the overall global paediatric mortality, representing an increasing proportion of all annual child deaths (37.4% in 1990, 46% or an equivalent of 2.6 Million deaths in 2016[1,2]). Decreases in neonatal mortality rates (NMR) have also shown similar regional variations, with reductions ranging from ~80% in eastern Asia, or ~50% in southern Asia (SEA) to ~40% in SSA in the same period[8]. The highest NMR are found in SSA (27.7 per 1000 Live births (LB) and in SEA (27.6 per 1000 LB), multiplying by 10 fold those documented in Europe (2.9 per 1000 LB)[7,8]. In the absence of changes in the current declining rates, it will be over a century before a newborn from SSA has the same survival probability as one born in Europe[7].

The first month of life is undeniably the most vulnerable period for the child's survival. Within these first four weeks, the risk is greatest at the very beginning of life, with up to three-quarters of all deaths occurring in the first seven days, and half of those in the first 24h[1,8,9]. Surviving therefore through childbirth and the

"golden first 28 days" appears therefore as a key milestone required to thrive and lead a healthy subsequent life. But, what makes the neonatal period such a critical moment? Why should a time period accounting for as little as 0.1% of the entire length of an average life (70 years), define more significantly the likelihood of surviving than any other time? There are multiple reasons that can account for this, but most of them gravitate around two premises: 1) The vicious circle established between poverty and disease, which appears very challenging to break and is particularly noticeable in this vulnerable period; and 2) the global disparities existing in terms of the quality of and access to health care[10], seriously jeopardized in those regions with less resources. If you add to the aforementioned fragile and weak health systems a myriad of diseases, particularly prevalent in those impoverished areas, then it is not difficult to understand why certain nations struggle to improve their health indicators.

More specifically, a healthy birth requires a previous healthy intrauterine development. For this, the pregnant mother needs to remain as healthy as possible, and a series of factors need to be controlled during the entire duration of gestation, and the *puerperium*. In rich countries, this is guaranteed by the constant control of the pregnancy, and the implementation of a series of preventive and therapeutic strategies designed to keep the dyad mother-child healthy. Comprehensive antenatal consultations are also capable of triggering actions that can accelerate an agile delivery should this become necessary. In poorer regions, antenatal care (ANC) consultations are increasing, although coverage rates are still far from reaching the current World Health Organization (WHO) recommendation of a minimum of four ANC visits[11]; and more importantly, the quality and availability of the health care interventions provided remains suboptimal. Similar challenges face the critical moment of childbirth, with coverage rates for deliveries attended by a skilled professional remaining insufficiently high, at a median of 65% during the period 2009- 2014[12]. Solving the maternal part of the equation responsible for neonatal outcomes requires starting by ensuring that maternal mortality rates also continue to globally decrease[13], in addition to heavily investing in improving the primary health care bottlenecks[14], and progressively implementing and scaling-up strategies that have already shown their cost-effectiveness in other settings of the world, or other innovative measures[14,15]. Not an easy task, or at least not one with immediate results. Such challenges are particularly blatant also in the context of stillbirths, the neglected victims of poverty, accounting for almost identical numbers of annual deaths to those occurring among newborns[16], and whose oblivion is finally starting to be adequately addressed in the global health agenda[6,17].

From the newborn's point of view, similar challenges can be expected in LMICs in relation to access to care, or quality of the preventive or therapeutic strategies available in country, leading to worsened health outcomes. However, the demographic explosion currently seen in SSA implies that this continent has become the principal birthplace of the world. Indeed, of the *circa* 130 million new babies born every year in the world, over 30% are already born in SSA, and this trend is expected to increase, with more than 1 in 3 children in the world expected to live in the continent by 2050[18]. Coverage rates of well-known and effective interventions to improve the care and health of the newborns are still lagging in

these settings, providing much room for improvement[7,12,17]. A simple but rather paradigmatic example has to do with the coverage of post-natal visits for babies, a clear WHO recommendation[19] that is only followed in a median of 28% of the births, globally[12]. How can you prevent, detect or treat disease, if you are missing nearly three quarters of all your target population? This is, indeed, the most neglected period for the provision of quality care[19].

A more philosophical issue with very significant practical implications also hinders our current understanding on how to count, prevent and treat those conditions prematurely killing newborns, and is linked to our fundamentally limited knowledge of what is really killing them. In addition to those "invisible" deaths[20] occurring at the community level outside the health system, and in the absence of functioning vital registration systems, there is a profound lack of knowledge of the real underlying causes for these deaths. According to the last global estimates in 2016, leading causes of death among newborns included preterm birth complications (35%), intrapartum-related events (24%), infectious diseases including sepsis/meningitis, pneumonia and tetanus (22%) and congenital disorders (11%)[2]. However, models utilized to build estimates for LMIC, where the vast majority of preventable deaths concentrate, have shown many flaws, and discrepancies in cause-attributable disease figures[21] have unraveled the shortfall of current methods, predominantly based on data derived from unreliable or poorly specific sources, including verbal autopsy or clinical records. The paucity of evidence-based data, and the obvious limitations of currently used methodologies to infer cause of death (CoD) in resource-constrained settings, warrant caution when interpreting current CoD estimates, at least if those are to be used for rational health planning and prioritisation decisions[22]. Innovation is key to overcome such limitations, and in this respect, more robust methodologies, such as the minimally invasive tissue sampling (MITS) post-mortem sampling techniques[23]. This technique has been validated against the reference complete pathological autopsy as a reliable CoD investigation tool in all age groups, -including newborns[24]-, and may appear as useful alternatives that can provide actionable and reliable data and thus contribute to better characterize mortality in this age group, and the necessary measures to specifically address it. Importantly, such methods are currently being implemented in sentinel sites across SSA and Asia, for perinatal and paediatric mortality surveillance through the Child Health and Mortality Prevention Surveillance Network (CHAMPS)[25,26]. Dissemination on an ongoing basis of the results of this ambitious and long-lasting project will surely contribute to better neonatal survival practices.

Irrespective of the said caveats regarding the precision and robustness of current estimates, infectious diseases are well-characterized contributors in LMIC to morbidity and mortality in the neonatal period[1,2,27]. In the newborn, some of these infections can be acquired in the community soon after birth, although the majority result from the vertical transmission of microorganisms from mother to child, either during gestation or at delivery, in particular bacteria, which are normal commensals or pathogens of the mother's genitourinary and gastrointestinal tracts. Important infectious clinical syndromes causing neonatal death include sepsis[28], meningitis and pneumonia. The microorganisms more frequently involved in serious infections in children younger than 3 months in

LMIC include, among others, group B Streptococcus (GBS)[29], Escherichia coli (*E. coli)*, *Listeria monocytogenes*, *Staphylococcus aureus*, other gram-negative bacteria, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, respiratory syncytial virus (RSV), *Neisseria meningitides* and *Bordetella pertussis*. However, in the context of the Human immunodeficiency virus (HIV) pandemic, many other microorganisms (including viruses, parasites or fungi) have emerged as important pathogens for the newborn. This information is relevant because for the majority of those neonatal infections, highly effective preventive or therapeutic strategies are available, and as a result of their implementation their burden in neonates from industrialized countries has been significantly reduced. As an example, *GBS* and *E. coli,* two well-known leading causes of neonatal morbidity and mortality, are vertically transmitted and particularly associated with early and late-onset neonatal sepsis, preterm birth and very-low-birth-weight delivery[30,31]. Overall case fatality rates associated to GBS in a global systematic review were 8.4%, peaking in SSA at 19%[32], precisely the place where highly effective prevention strategies such as intrapartum antibiotic prophylaxis (IAP) have not been implemented due to the scarcity of laboratory support and the fragility of the health systems[30]. *E. coli* is considered the most frequent cause of invasive bacterial infection in preterm infants and to date, no prevention measures have been developed[33]. Other infectious diseases also considered as important contributors to neonatal mortality include infections encompassed under the TORCH syndrome. Among them, congenital cytomegalovirus (CMV) infection is the most prevalent, but also remains majorly neglected in both the developed and developing world[34], with its real burden and impact being largely unknown[35]. An interesting approach to prevent many of these neonatal infections now includes maternal vaccination during pregnancy[36], under the assumption that maternal transfer of antibodies to the newborn will be more feasible, effective and rapidly protective than waiting for the generation of neonatal immune responses to vaccines administered directly to them. This "vertical vaccination" strategy has already been successfully implemented for tetanus and pertussis control, and is currently being explored for several other pathogens, including GBS, RSV, Flu and *S. pneumoniae*[37].

Other major well-characterized non-infectious causes of neonatal death include preterm-birth complications, intrapartum–related complications and congenital abnormalities. Births that follow spontaneous preterm labour usually are the consequence of specific maternal factors, including pregnancy specific complications (hypertension, diabetes, malnutrition), infections, and other non-preventable causes[38]. Some of these causes, as previously mentioned, can be proactively screened for during ANCs clinics and easily managed. Intrapartum-related complications, often leading to life-threatening perinatal asphyxia, are however more difficult to prevent, and their management is highly dependent on the availability of skilled staff attending the delivery [39]. Congenital abnormalities are much harder to prevent, particularly in the absence of early ultrasound screening for pregnancies, a strategy poorly implemented and often unavailable in LMICs. Such congenital abnormalities, however, may be preventable in some cases (for instance by providing folic acid supplementation during pregnancy), and may occur more frequently in those countries with high levels of consanguineous partnerships[39]. Finally, other well-known but moderately neglected (likely due to their multifactorial aetiology) causes of neonatal mortality include metabolic

disturbances such as hypoglycaemia[40]. Again, limitations in the availability or usage of cheap diagnostic tools for its diagnosis, hinders the adequate recognition of simple complications that in the absence of a rapid detection and correction become rapidly lethal.

CONCLUSIONS

The specific neonatal mortality SDG target aims to reduce NMRs to a maximum of 12 per 1000 live births in every country of the world by 2030[5]. The SDGs offer also an international collaborative platform of international consensus to advance together towards the global achievement of these goals. The wider ambitions of the SDGs in comparison to the MDGs cannot dilute the importance of health and child survival in these new objectives. Importantly, in the absence of an accelerated progress in neonatal mortality, the world will fail to significantly reduce overall child mortality. Universal coverage of essential interventions has the potential to reduce neonatal deaths by an estimated 71%, benefit women and children after the first month, and reduce stillbirths[14]. Particular support, attention and stewardship to LMICs, which have the greatest needs -but also the tiniest resources- will be critical so as to enhance the uptake and scale-up of these interventions, in an equitable manner. If every country achieves the SDG target for neonatal survival by 2030, approximately 5 million neonatal lives will be saved throughout the period 2017–2030[8] and all of the efforts concentrated in helping newborns go through the arid and sinuous "golden first 28 days of life" will have been worthwile.

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