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## Global efforts needed to address burden of preventable stillbirth

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The global stillbirth rate in 2021 was 13.9 per 1,000 total births according to the United Nations Inter-Agency Group for Child Mortality Estimation (UN-IGME).<sup>1</sup> That translates into one stillbirth every 16 seconds, with over 40% occurring during labor,<sup>2</sup> bringing the tragic toll to almost 2 million babies stillborn every year. Low- and lower-middle income countries are overrepresented in stillbirths, accounting for 84% of all stillbirths but only 62% of all livebirths, with 3 in 4 stillbirths occurring in sub-Saharan Africa or Southern Asia (Figure 1a). The proportion of global stillbirths occurring in sub-Saharan Africa increased from 26% in 2000 to 45% in 2021; this stillbirth rate of 21.0 per 1,000 total births was seven times higher than the lowest regional rate of 2.9 found in the combined Europe, Northern America, Australia and New Zealand region. Of South Asian countries, Pakistan has the highest stillbirth rate (30.6 per 1000 total births) (Figure 1a) but, even within Pakistan, there are significant regional discrepancies, with some regions reporting stillbirth rates double the national rate.<sup>3</sup>

During the COVID-19 pandemic, maternal and fetal outcomes deteriorated substantially.<sup>4</sup> The limited data that exist for 2021 showed no significant excess mortality in children or adolescents, but documented evidence of increased stillbirths.<sup>5</sup> A recent study identified an increase in stillbirths during the first month of lockdown in high-income countries (HICs) and, in Brazil, an upper-middle income country, higher stillbirth rates were observed for up to 4 months after lockdown compared to pre-lockdown rates.<sup>6</sup> In England and Wales, stillbirth rates increased from 3.8 per 1,000 total births in 2020 to 4.1 in 2021, which is higher than the prepandemic rate of 3.9 in 2019.<sup>7</sup>

In the United States, although the number of livebirths increased by just 0.7% between 2020 and 2021, stillbirths increased by 2.3% during the same period,<sup>8</sup> raising concerns about an urgent need for an action plan to monitor the factors that caused this major public concern.<sup>9</sup> In Israel, another HIC, where no stillbirth data were reported for 2021, the stillbirth rate increased from 4.4 in 2019 to 5.4 in 2020 (Figure 1b).<sup>10</sup> An important unknown is whether the increase in stillbirth rates were aligned with maternal mortality rates during the pandemic. In 2020, for example, around 1000 women in the World Health Organization (WHO) European Region died of complications related to pregnancy or childbirth,<sup>11</sup> but delays in reporting and significant discrepancies among national databases confound estimation of the true burden of stillbirths in Europe and, consequently, understanding the risk factors associated with stillbirths in different countries.<sup>12</sup> In Germany, during 2016-2021 the stillbirth rate showed an upward trend of 17% (from 3.66 to 4.28 per 1000 births),<sup>13</sup> and, in Greece, a 7.4% annual increase during the same period drove the stillbirth rate to 5.3 per 1000 births in 2021 (Figure 1b).<sup>14</sup>

In some HICs with more robust surveillance systems, such as Canada and Australia, fetal death rates remained stable between 2019 and 2021. In Canada, fetal deaths are registered when the gestation is  $\geq 20$  weeks or birthweight is  $\geq 500$  grams, while stillbirths specifically refer to fetal deaths with gestation  $\geq 28$  weeks.<sup>15</sup> Using these definitions, the fetal death rate in Canada changed little from 8.5 in both 2019 and 2020 to 8.6 in 2021, whereas stillbirth rates fluctuated between 2.84, 2.78 and 2.86 in 2019, 2020 and 2021, respectively.<sup>16</sup> In Australia, where stillbirths are defined as death of a baby at  $\geq 20$  weeks' gestation or with a birthweight  $\geq 400$  grams, the fetal death rate increased from 7.2 in 2019 to 7.7 in 2020 but decreased to 7.0 per 1000 births in 2021.<sup>17</sup> It is only with such detailed reporting that the impact of pandemic lockdowns and interventions in individual countries might be disentangled from background trends. With countries using differing definitions for reporting stillbirth versus fetal death, the WHO recommends that, for international comparisons, stillbirth should be defined as fetal birth with no signs of life and a birthweight of  $\geq 1000$  g or gestation at birth  $\geq 28$  weeks.<sup>18</sup>

Although the global stillbirth rate has declined by 35% over the past two decades from 21.3 stillbirths per 1,000 total births in 2000 to 13.9 in 2021, this reduction still lags behind other mortality indicators.<sup>1</sup> The 2000–2021 annual reduction rate (ARR) in mortality for children aged 1–59 months, for example, was double the ARR in stillbirths for the same period (4.0% versus 2.0%, respectively).<sup>1</sup> The UN-IGME 2020 report on the global burden of stillbirths recorded 48 million stillbirths in the past two decades. This report estimates that, if current trends continue, the world will suffer an additional 20 million stillbirths before 2030. UNICEF's roadmap Every Newborn Action Plan (ENAP) calls for each country to achieve a stillbirth rate of 12 or fewer per 1000 total births by 2030, and to close equity gaps.<sup>19</sup> However, major challenges remain even in the adequate assessment of the scale of the issue.<sup>19</sup> ENAP-Ending Preventable Maternal Mortality (ENAP-EPMM) data reveal that while 98% of countries reported birth registrations, only 61% of countries have a stillbirth registration policy.<sup>18</sup> Overall, 90% of countries have a maternal and perinatal death surveillance and response (MPDSR) system in place for maternal deaths and 77% for neonatal deaths, but only 58% have surveillance for stillbirths.

Several risk factors of stillbirth, including causal genetic variants have been identified,<sup>20,21</sup> yet in numerous cases, the cause remains elusive. In 2003 the National Institute of Child Health and Human Development (NICHD) in the US, initiated the Stillbirth Collaborative Research Network (SCRN) to investigate the possible factors underlying stillbirth.<sup>22</sup> Having investigated over 500 stillbirths across 59 US medical centres, over a span of five years, the results showed that in nearly 25% of these instances, researchers could not ascertain probable or possible cause of death, whereas many stillbirths exhibited multiple potential causes.<sup>22,23</sup> Systematic

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reviews and research have highlighted that potential causes of stillbirth include complications during pregnancy and labour (e.g., preterm labour, twin pregnancies, placental abruption), placental issues (such as inadequate blood flow), fetal genetic problems and birth defects (e.g., anencephaly), maternal or fetal infections (including group B streptococcus), umbilical cord problems (such as knots), high blood pressure disorders (including chronic hypertension and preeclampsia), and medical conditions in pregnant individuals (e.g., pre-pregnancy diabetes). According to the latest UK MBRRACE report, stillbirths due to congenital anomalies represent under one-tenth of stillbirths, the proportion of unexplained stillbirths has reduced over time, but one-third of stillbirths still fall into this category (33% in 2020), whereas an increasing proportion of stillbirths were due to placental causes over time (35% in 2020).<sup>24</sup> Unfortunately, in the HIC such as UK, the effect of ethnicity and deprivation is also evident on stillbirth rates<sup>24</sup>, which were lowest for babies of White ethnicity from the least deprived areas (2.78 stillbirths per 1,000 total births and 1.26 neonatal deaths per 1,000 live births). The combined impact of ethnicity and deprivation was highlighted by a stillbirth rate of 8.10 and 7.96 per 1,000 total births for babies of Black African and Black Caribbean ethnicity respectively from the most deprived areas.<sup>24</sup>

Addressing the global stillbirth challenge demands a comprehensive strategy that extends beyond obstetric surveillance and incorporates the latest findings of studies targeted at reducing stillbirth rates. These strategies should prioritize healthcare interventions, including fetal monitoring and labor induction for high-risk pregnancies by healthcare professionals, skilled attendance during childbirth and improved intrapartum care. Furthermore, strategies must focus on monitoring women with a history of stillbirth and strengthening stillbirth surveillance. Prevention of infections, such as infection control for malaria, or through measures like syphilis testing during the first antenatal appointment and routine CMV serologic tests for pregnant women, should also be considered. To further reduce stillbirth rates, promoting public health measures, such as cessation of drinking and smoking after the first trimester, improved nutrition management, as well as managing air quality and ambient temperature exposure, are vital components of these efforts. Research findings from studies investigating potential interventions are listed in Table 1.

This comprehensive strategy should also involve better access to healthcare services. Moreover, it should improve health education of mothers to increase awareness of warning signs and prompt reporting. It is equally important to invest on research into unexplained stillbirths and to support health professionals to communicate findings to mothers and bereaved family members. This multifaceted approach will address the critical need for data collection and research and development to gain a deeper understanding of the risks and

causes associated with stillbirth, enabling the development of more efficient interventions for high-risk pregnancies. International collaboration is another crucial element of this strategy (Figure 2).

In the most optimistic ENAP scenario, if every country's stillbirth rate reached or fell below the current average rate in HICs (i.e., 3 stillbirths per 1,000 total births) by 2030, almost 8.4 million babies' lives could be saved. Thus, global efforts by researchers, health professionals and national health systems are urgently needed to provide accurate data on stillbirths which would enable better data analysis and comparison. Above all, we need immediate and sustained measures to provide high-quality care to pregnant women, address the burden of preventable stillbirths, and close equity gaps in stillbirth rates globally

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## FIGURE LEGENDS

**Figure 1.** (a) The United Nations Inter-Agency Group for Child Mortality Estimation (UN-IGME) stillbirth rate (SBR) estimates<sup>39</sup> for Pakistan, Somalia, Mali, Sierra Leone, Bangladesh, Ethiopia, Kenya, Mozambique, South Africa, India and Brazil for 2017-2021. (b) SBR data for 2017-2021 according to national definitions for United States<sup>40</sup>, UK<sup>7</sup>, Greece<sup>41</sup>, Germany<sup>13</sup>, Australia<sup>17</sup> and Canada<sup>16</sup> for 2017-2021.

**Figure 2.** A comprehensive approach that extends beyond enhancing obstetric surveillance to address the global burden of stillbirth.

**Table 1.** Examples of findings of studies monitoring key healthcare interventions targeting stillbirth, such as obstetric management approaches, infection testing and control and public health strategies.

Intervention and/or Surveillance Results	Findings	Study Design	Target Population	Source
Biweekly Fetal monitoring from 39 weeks' gestation	64% reduction in term stillbirth	Cohort study of women who gave birth between Jan 2016 and Dec 2020, receiving antenatal care at Victoria Australia	South Asian-born women	24
Induction of labour at 41+0 to 41+1 weeks	Reduced stillbirths (adjusted odds ratio [aOR] 0.15, in both nulliparous and multiparous women.	Registry-based Dutch cohort study; 2010 to 2019	239 971 low-risk singleton pregnancies; birth from 41+0 to 42+0 weeks	25
Induction of labour at 39 weeks of gestation in women with low-risk pregnancies	IOL with birth at 39 weeks was associated with a small reduction in the risk of adverse perinatal outcomes	National cohort study in England	All English National Health Service (NHS) hospital births between January 2018 and March 2021	26
Risk and characteristics of antepartum versus intrapartum stillbirths in the U.S.	Risk of intrapartum versus antepartum stillbirth higher among those without prior live birth, relative to those with at least one prior live birth (RR 1.32); risk higher in those with gestational hypertension, relative to those with no report of gestational hypertension (RR 1.47)	Cross-sectional singleton births study (24–43 weeks) using 2014 U.S. Fetal Death and Natality data from National Center for Health Statistics	National Center for US Health Statistics	27
Monitoring by Health Professionals & skilled attendance at childbirth	Increasing access to skilled attendance at childbirth is one of the evidence-based recommendations for reducing stillbirths in Sub-Saharan Africa (SSA)	Systematic review	Studies in 18 SSA countries	28
Stillbirth surveillance	Most common causes of stillbirths were hypertensive disorders of pregnancy (27.6%), antepartum haemorrhage (19.5%), and congenital anomalies (9.3%)	Single-Tertiary Care Referral Institute	Northern India	29
Obstetric Monitoring	Managing obstetric intrahepatic cholestasis, maternal anti-helminthic treatment, and intermittent preventive treatment of malaria, showed promise in reducing stillbirth rates; need further study. Periodont disease: clear risk stillbirth factor, but no targeted interventions reduced stillbirth rates. Need for randomised trials	Systematic review of evidence for 16 antenatal interventions	Interventions deliverable at community level in low-/middle-income countries	30

Enhancing preterm birth detection, managing SGA, improving intrapartum care, monitoring women with stillbirth history, breech births, and high-risk referrals	Risk factors: Maternal age $\geq 35$ years (aOR: 1.82), extreme prematurity (aOR: 3.29), moderate prematurity (aOR: 2.45), small-for-gestational age (aOR: 2.32), breech/transverse births (aOR: 3.84). Caesarean section reduced odds (aOR: 0.50). Abnormal vaginal discharge (aOR: 1.42) and stillbirth history (aOR: 3.08) increased odds	Cross-sectional 2017-2020 study at National Maternal and Child Health Centre	Cambodia	31
Management of Nutrition	Balanced energy/protein supplementation versus no supplementation suggests a probable reduction in stillbirth (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.39 to 0.94	Cochrane Database of Systematic Reviews (search date: 29 February 2020)		32
Syphilis testing at first antenatal appointment	39.4% reduction in stillbirth after introduction of routine syphilis testing at first antenatal appointment	2001 - 2015 Cohort study	China	33
CMV serologic tests as part of regular testing in pregnant women	86.6 per 1000 pregnancies in Maternal CMV infection group, vs 7.8 per 1000 pregnancies in non CVM infected group. Significant difference (RR 12.17) that remained so even correcting for birth defects (RR 9.38)	Prospective, hospital-based cohort study	China	34
Pregnancy outcomes in women screened for tuberculosis infection in Swedish antenatal care	In total, 7,408 women with 12,443 pregnancies were included and in multivariable analysis, stillbirth (adjusted Odds ratio [AOR] 1.90, 95% confidence interval [CI] 1.13-3.21, $p=0.016$ ), was significantly associated with tuberculosis infection.	Pregnancy outcomes & QuantIFERON results linked to data from the Swedish Pregnancy and Patient Registers	<10 years immigration history from TB-endemic countries	35
Drinking and smoking cessation after first trimester of pregnancy	Dual exposure to drinking and smoking after first trimester associated with 2,78 times risk of late stillbirth	Prospective cohort study, data collection between Aug. 2007 and Jan 2015	Cape Town, South Africa, US	36
Smoking Cessation	Smoking associated with 47% increase in odds of stillbirth. In subgroup analysis, smoking 1-9 cig/day and $\geq 10$ cig/day was associated with a 9% and 52% increase in stillbirth odds, respectively. Studies defining stillbirth at $\geq 20$ , $\geq 24$ , and $\geq 28$ weeks showed 43%, 58%, and 33% higher odds of stillbirth for smoking mothers compared to non-smoking mothers.	Meta-analysis	21 cohorts, 8 case controls and 5 cross sectional studies	37
Managing ambient temperature exposure	Overall, Stillbirth risk increased after chronic exposure to ambient temperatures below $15^{\circ}\text{C}$ , with highest risk at $29.4^{\circ}\text{C}$	Systematic Review 42,848 stillbirths among 3.4 million births	Seven countries	38



