REVIEW

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A landscape analysis of preterm birth in South Africa:

systemic gaps and solutions

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Lack of accurate nationally representative preterm birth estimates limit our epidemiological understanding of this syndrome and the extent to which health services can respond appropriately.

The World Health Organization defines preterm birth (PtB) as delivery before 37 completed weeks of gestation. PtB affects 15 million infants worldwide annually. In 2014, Asian and sub-Saharan African regions accounted for 81.1% of this burden. The true national burden of PtB in South Africa is unknown: current estimates rely on hospital mortality data and projections. Furthermore, current estimates are subject to bias as gestational age is mostly estimated using the last menstrual period and symphysis-fundal height measures instead of an early ultrasound. Lack of accurate nationally representative PtB estimates limits our epidemiological understanding of PtB, and the extent to which health services can respond appropriately.

Using data obtained from national data sets, e.g. the Perinatal Problem Identification Programme, experts, and published papers, this chapter highlights the estimated global, regional and local burden of PtB, challenges with measuring gestational age, PtB-associated complications, and optimal care packages. The chapter also addresses key interventions that prevent and predict PtB, and interventions to manage preterm infants.

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Introduction

The World Health Organization (WHO) defines preterm birth (PtB) as delivery before 37 completed weeks of gestation, or fewer than 259 days from the first day of a woman's last menstrual period.[1] This syndrome affects 15 million infants worldwide annually, with implications for short- and long-term morbidity, mortality and socio-economic liability.[2] Global PtB estimates were 9.8% in 2000,[3] 9.6% (2005), 11.1% (2010)[4] and 10.6% (2014).[3] Low- and middle-income countries (LMICs) bear the burden of PtB (81.1% of PtB occurs in sub-Saharan Africa and South Asia). The PtB burden in South Africa is unknown. Modelled estimates reported it at 8 per 1 000 live births in 2010[4] and 12.4 (uncertainty range 8.6 - 17.1) per 1 000 live births in 2014.[3]

This chapter addresses challenges with estimating PtB burden at population level; PtB classification systems; associated morbidity and mortality; and care packages. Key recommendations are made at the end of the chapter.

Challenges with population-level estimations of preterm births

PtB estimation is complicated by lack of data availability, and inconsistency between PtB definitions across sites.[3,5]

In LMICs, data from national civil registration and vital statistics (CRVS) systems and national research studies are not collected routinely, thus country-level PtB estimations rely on the few non-representative research studies. Therefore, global PtB estimations are influenced disproportionately by high-income countries (HICs) with robust monitoring systems. South African PtB estimates were derived from two studies in 2010[6,7] and four studies in 2014.[8-10] However, determining PtB incidence was not the primary research objective in these studies, necessitating cautious interpretation of the estimates.[11]

The WHO PtB definition includes all live births (births with "any signs of life within the first hour of life").[12] While the upper gestational age (GA) cut-off (<37 weeks) is well defined, the lower limit varies depending on the limit of viability (20 - 28 weeks), i.e. the GA at which 50% of infants born will have a reasonable chance of survival.[13] This limit depends on availability of interventions for extremely preterm births (ePtB) (<28 weeks GA) or extremely low birth weight (ELBW) neonates (<1 000 g). In well-resourced HICs the ePtB survival rate has increased significantly,[14-16] decreasing the limit of viability to ~24 or 25 weeks. In a LMIC such as South Africa, this limit is >27 weeks' GA. Therefore, no uniform international GA cut-off point exists to define viability, restricting direct comparability of PtB rates across settings.[2]

Other definitional problems include misclassification stemming from two challenges, namely errors in GA assessment and reporting, and misclassification of live births as stillbirths.[17-20]

Assessing and classifying preterm birth

PtB is a complex syndrome with varying phenotypes.[21] Traditional classification systems stratify PtB according to GA, clinical presentation, and pathophysiological pathways.[20,22] Classifications based on GA are most commonly used because GA correlates strongly with foetal maturity and all developmentally regulated processes and is a good predictor of short- and long-term outcomes.[23]

Classifying preterm birth by gestational age

In addition to the arbitrary PtB definition of <37 completed weeks,[24] further subdivisions distinguish ePtB, very early PtB (28 - <32 weeks), moderate PtB (32 - 34 weeks), and late PtB (34 - 36 weeks).

GA can be determined according to pregnancy duration from date of last menstrual period (LMP), foetal size assessed using ultrasonography or symphysis-fundus height (SFH) measurements or postnatal clinical assessment methods. GA assessments performed earlier in pregnancy are more accurate, with early antenatal ultrasound (<24 weeks) considered the gold standard (accuracy of ±5 - 7 days).[25] In LMICs, ultrasonography access tends to be limited to tertiary-level facilities and private practice, and first antenatal care (ANC) bookings are usually in the second trimester. Therefore, most pregnancies are dated using the LMP, SFH and postnatal clinical assessments, which may be incorrect by four weeks or more compared with ultrasonography.[25] A recent pregnancy cohort study in a routine primary healthcare facility in the Western Cape showed variations in GA assessment resulting in significantly different PtB incidences when LMP (36%), SFH (17%), and ultrasound (11%) methods were used.[26]

Where GA data are not available, particularly in resource-limited settings,[27] proxy postnatal measures are used, such as low birthweight (LBW), birthweight <2 500 g, or foot length.[28] Although these are useful to guide clinical management, they are less useful for accurately determining PtB status as a proportion of LBW infants are intrauterine growth restricted (IUGR) full-term infants, and thus small-for-gestational age (weight less than the 10th percentile for sex and GA) (SGA).[29] Furthermore, infants born ≥2 500 g are not all full term.[30] Consequently these proxy measures fail to distinguish between infants born too small (constitutionally small but normal, or pathologically small at term because of IUGR) and those born too soon (i.e. PtB), outcomes that have different aetiologies.[31]

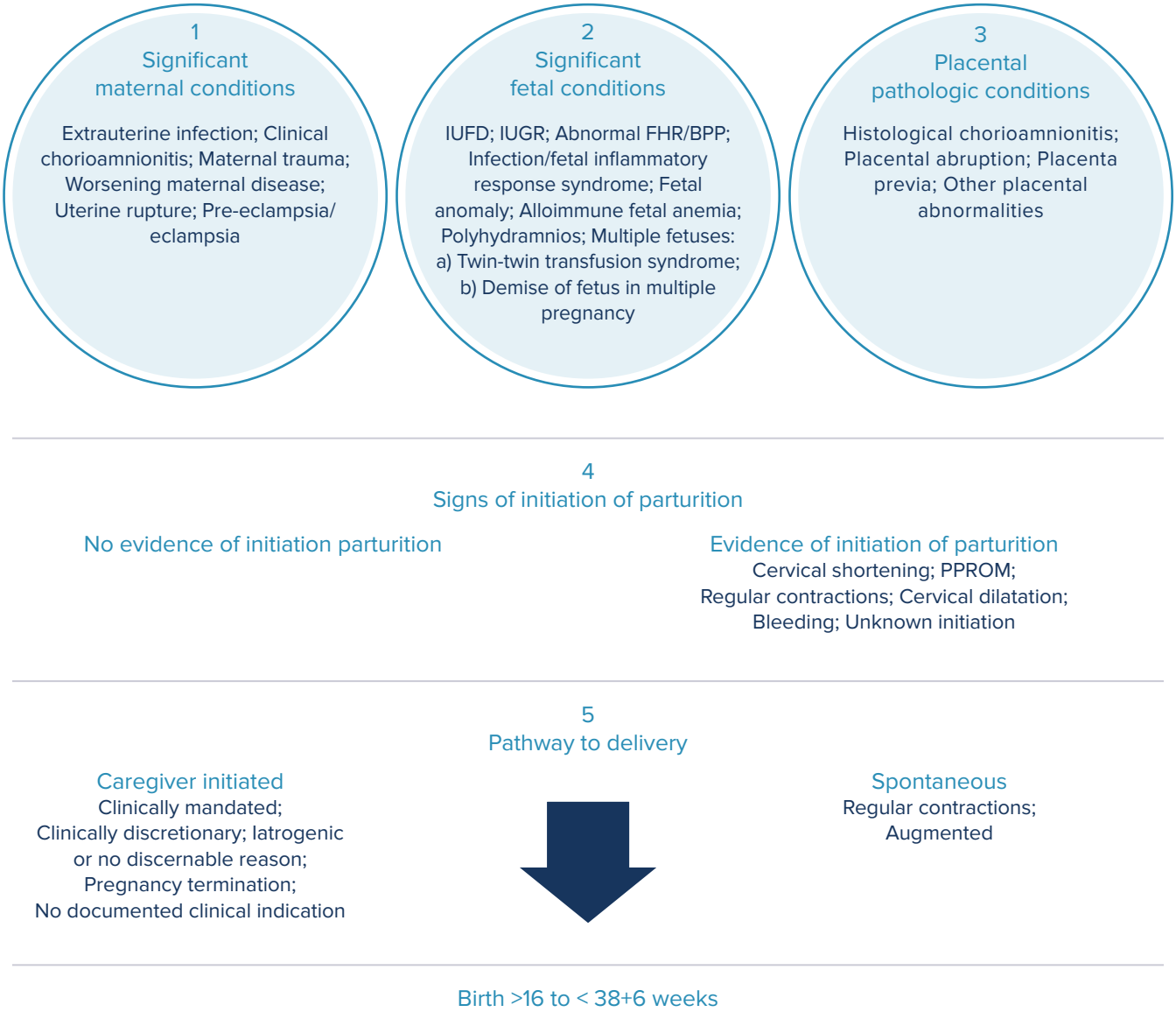
Determining preterm birth: phenotypic classification

PtB can be classified phenotypically[32,33] into spontaneous and medically indicated PtB. These have considerable aetiological heterogeneity needing different screening, prevention, and treatment strategies.[34] Spontaneous PtB (SPtB) can be due to preterm labour (PTL), with cervical dilation or preterm prelabour rupture of membranes (PPROM). Medically indicated PtB through labour induction and/or caesarean delivery are frequently due to maternal factors (e.g. preeclampsia) or foetal factors (e.g. IUGR and foetal distress).[22,35,36] Classification can also be based on placental pathology and postulated physiological mechanisms.[20]

Villar and colleagues proposed a five-component phenotype classification that distinguishes between SPtB and medically indicated PtB (Figure 1).[33]

Subsequently, a nine-phenotype SPtB classification system was developed to facilitate identification of more specific aetiologies, namely infection/inflammation, decidual haemorrhage, maternal stress, cervical insufficiency, uterine distention, placental dysfunction, PPROM, maternal co-morbidities, and familial factors.[32] However, given the human and infrastructural capacity required to apply this classification it is better suited to well-resourced settings or research studies.

Figure 1: A comprehensive, sophisticated phenotypic classification system to improve understanding of the preterm birth syndrome



Source: Villar et al., 2012.[33]
BPP = biophysical profile; FHR = foetal heart rate; IUFD = early intrauterine foetal death; IUGR = intrauterine growth restriction; PPROM = preterm premature rupture of membranes.

Morbidity in preterm infants

In LMICs, the exact prevalence of PtB, ePtB and ELBW infants is not known. Estimates are that 12.4 per 1 000 live births are preterm; fewer will be ELBW. PtB and ELBW infants are at risk of morbidity and given the Sustainable Development Goals (SDGs)[37] and Global Strategy for Women's, Children's and Adolescents' Health,[38] efforts are needed to ensure that children survive and thrive. In South Africa, a hospital-based retrospective study showed short-term adverse outcomes among PtBs, such as respiratory distress syndrome, necrotising enterocolitis, bronchopulmonary dysplasia, intraventricular haemorrhage, sepsis, feeding difficulties, and auditory and visual difficulties.[39] No studies have documented medium-to-long-term outcomes of PtB, highlighting a key gap in the guidance of medium - and long-term prevention, care and treatment.

Mortality in preterm infants

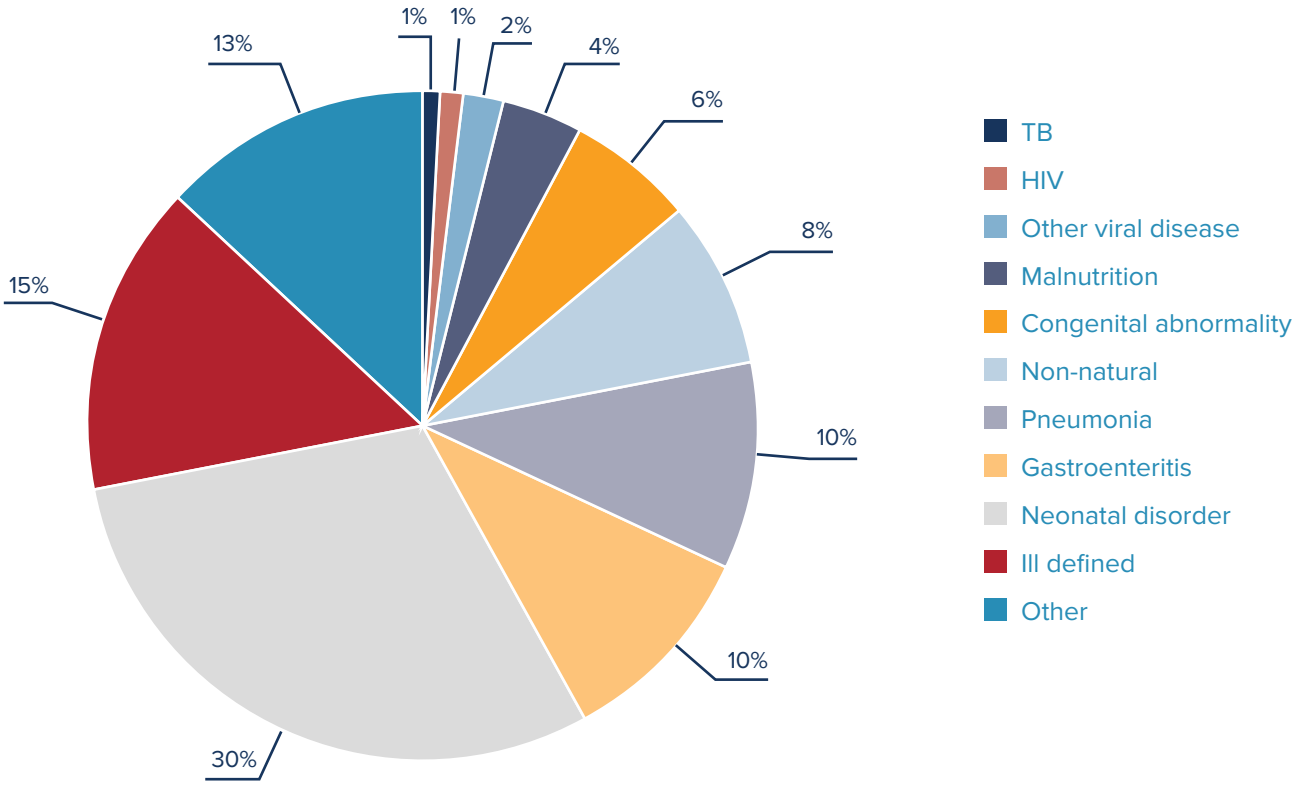
Preterm birth complications form one of the leading causes of under-five mortality (U5M) globally,[40] and the leading cause of neonatal deaths (NNDs),[41] accounting for 14.4% of U5M in 2015 (Figure 2).[42] Neonatal deaths are also indirectly caused by LBW, a product of PtB and/or SGA.[43] Data also show that regardless of weight, most stillbirths are unexplained, whereas most early NNDs are due to SPtB, particularly in the 28 - 33-week period (Figure 3).

A major cause for concern is that since 2000, the overall neonatal mortality rate (NMR) has remained unchanged (Figure 4). In South Africa, the NMR among newborns weighing >1 000 g declined from 8.8/1 000 live births in 2000 - 2002 to 8.5/1 000 in 2015 - 2017, which is close to the South African target of 8/1 000 livebirths[44] (Table 1).

These data highlight the success of improved intensive care for infants weighing >1 000g. However, ELBW infants constitute 60% of PtB mortality in South Africa.[45] Among ELBW infants, survival is highest if birth weight is >900g, while survival is <60% if birthweight is <800 g, even in well-resourced tertiary hospitals (Table 2).

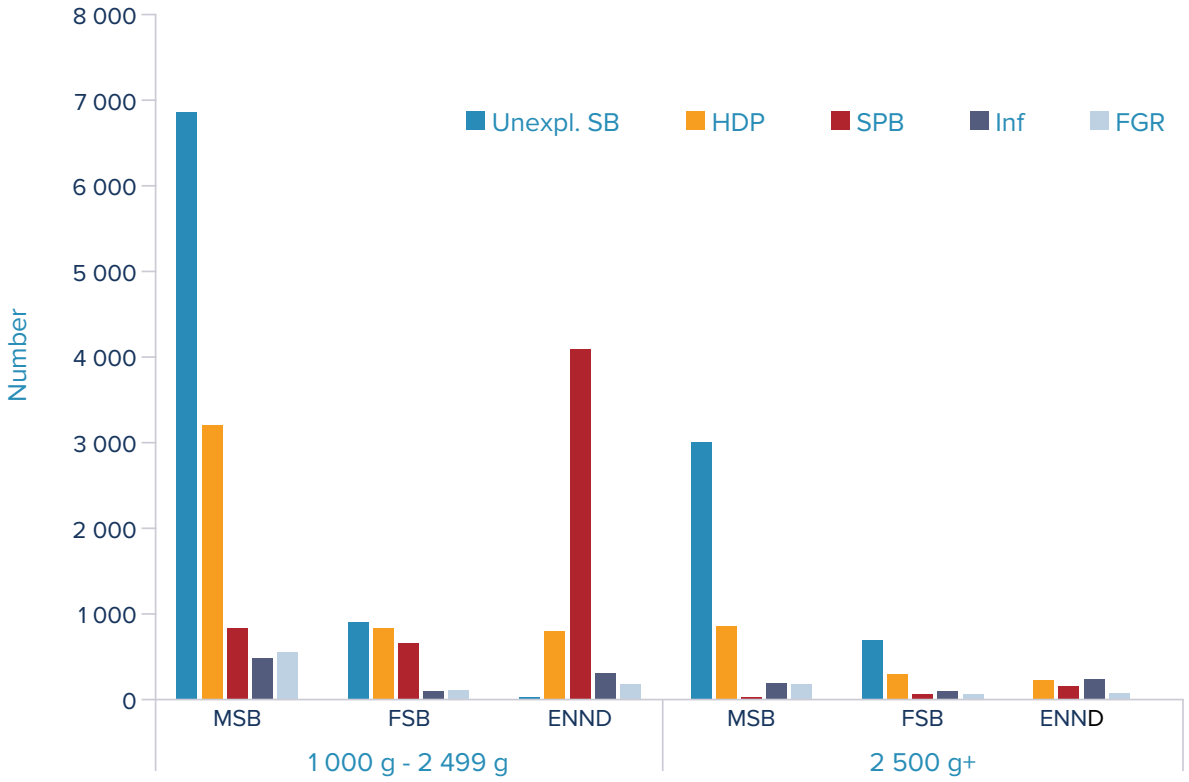
Given current resource constraints, and demand for neonatal intensive care beds, it is unlikely that the South African public health system has the capacity to provide highly resource-intensive specialised care for VLBW infants. Their survival depends on timely referral to facilitate delivery in tertiary settings, necessitating a responsive and expansive health system.[46] Particularly in rural settings, such as Limpopo and Mpumalanga provinces, neonatal survival rates depend on the quality of district-level neonatal care.

Figure 2: Causes of death in children aged under five years in South Africa, 2015



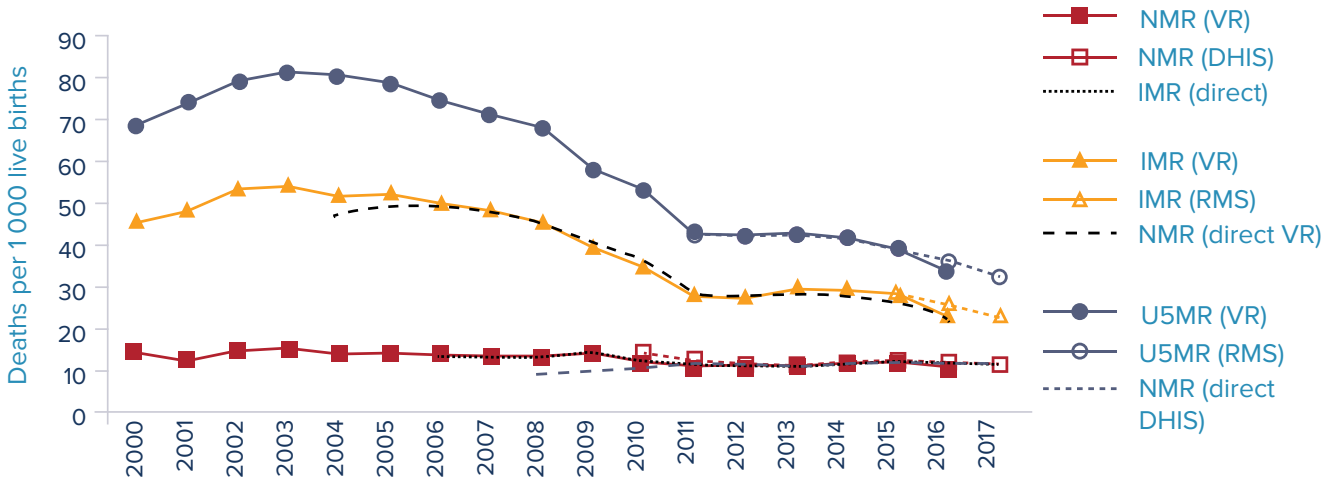
Source: NDoH, 2017.[42]

Figure 3: Comparison of stillbirths and early neonatal mortality per weight category, South Africa, 2015 - 2017



Source: Perinatal Problem Identification Programme (PPIP): 2015 - 2017.[a]
ENND = early neonatal death; FGR = foetal growth retardation; FSB = fresh stillbirth; HDP = hypertensive disorders of pregnancy; Inf = infection; MSB = macerated stillbirth; SPB = spontaneous preterm birth; Unexpl. SB = unexplained stillbirth.

Figure 4: Under-five, infant and neonatal mortality rates in South Africa, 2000 - 2017



Source: Dorrington et al.; 2019.[44]
DHIS = District Health Information Software; IMR = infant mortality rate; NMR = neonatal mortality rate; RMS = rapid mortality surveillance; U5MR = under-five mortality rate; VR = vital registration.

a Personal communication: Robert Pattison, PPIP, 10 April 2019.
Note: PPIP (https://www.ppip.co.za/) is an audit tool for perinatal mortality at facility level and captures data for 80% of national public sector deliveries and mortality.

Identifying risk factors for preterm birth

In South Africa, key maternal factors for both SPtB and medically indicated PtB include smoking, alcohol and illicit drug use, low socio-economic status, and illegal termination of pregnancy (Figure 1). Hypertensive disorders of pregnancy (HDP) are also strongly associated with SPtB and stillbirths (Figure 3). Furthermore, 30.8%[47] (approximately 300 000 live births annually)[48] are HIV-exposed in South Africa, increasing the risk of PtB in HIV-exposed compared with HIV-unexposed children secondary to HIV infection,[49,50] or maternal antiretroviral treatment (ART) regimens, especially those including protease inhibitors.[51,52] Data also indicate that HIV-positive women on ART have more HDP, such as pre-eclampsia,[53] and suggest that this may be due to immune reconstitution due to ART.[54] Further research, using rigorous study designs with robust measures and procedures, such as prospective cohort studies, is required to understand the interaction between exposure to maternal HIV/ART and PtB.

Clinical and public health interventions to prevent and manage preterm birth

While South Africa does not have a stand-alone PtB policy, the Strategic Plan for Maternal, Newborn, Child and Women's Health (MNCWH) and Nutrition in South Africa 2012 - 2016 included key interventions for saving the lives of mothers and infants (Box 1).[55] Given the complex interaction of risk factors, prevention and prediction of PtB and management of short and long-term health effects requires a suite of interventions that must commence pre-conception (Table 3).[56,57]

Some recommended actions (e.g. kangaroo mother care (KMC) for LBW infants) are applicable to PtB infants. Box 2 describes the implementation of KMC as an illustrative example.

Table 1: Stillbirth, perinatal and neonatal mortality rates among children with birthweights >1 000 g in South Africa, 2000 - 2017

Period	Perinatal mortality rate (/1 000)	Neonatal mortality rate (/1 000)	Early neonatal mortality rate (/1 000)	Late neonatal mortality rate (/1 000)	Stillbirth rate (/1 000)
2000 - 2002	26.3	8.8	8.1	0.7	18.4
2003 - 2005	25.8	9.1	8.1	0.9	17.8
2006 - 2008	25.6	9.9	8.3	1.6	17.4
2009 - 2011	25.9	9.7	8.1	1.6	17.9
2012 - 2014	23.6	8.3	7.0	1.3	16.7
2015 - 2017	22.6	8.5	6.6	1.9	16.1

Source: PPIP. Note: PPIP does not capture GA so data are reported in birth weight categories.
Personal communication: Natasha Rhoda, University of Cape Town, 30 July 2019.

Table 2: Percentage survival to discharge among VLBW infants in selected tertiary hospitals in South Africa, 2000 - 2009[a]

Birth weight	Year	Survival to discharge (percentage)	Hospital
800 - 899 g	2000 - 2002	37%	Chris Hani Baragwanath, JHB
	2006 - 2010	38%	Charlotte Maxeke Academic, JHB
	2017	69%	Tygerberg Hospital, Cape Town
		64%	Groote Schuur Hospital, Cape Town
750 - 900 g	2013	52%	Charlotte Maxeke Academic, JHB
500 - 749 g	2007 - 2009	56%	Tygerberg Hospital, Cape Town

Source: Ballot et al., 2015.[39]
VLBW = very low birth weight.

a Personal communication: Dr Lloyd Tooke, University of Cape Town, and Professor Johannes Smith, Stellenbosch University, 20 May 2019.

Antenatal steroids have been shown to reduce neonatal mortality by 30% and to decrease the complications of PtB, including bronchopulmonary dysplasia, respiratory distress syndrome and necrotising enterocolitis.[46]

Table 3 includes an additional set of high-impact, low-cost interventions currently being implemented in the South African healthcare system. The current coverage rate for essential newborn care interventions is unknown, including interventions targeted at PtB infants.

Table 3: Interventions identified in the literature to predict, prevent and manage preterm birth optimally

Location	Type of intervention			
	Prediction	Prevention	Management of PtB	Management of preterm infants
At all levels from community to health facility		• Prevent unwanted pregnancies and promote pre-conception health • Interventions for alcohol and illicit drug use • Health promotion interventions to address chronic diseases; and HIV and STI prevention, screening and management • Nicotine replacement therapy	• In utero transfer to health facilities with a NICU • Skilled birth attendants • Family/partner support during labour	• Cord care and delayed cord clamping • Kangaroo Mother Care • Hypothermia prevention • Exclusive breastfeeding support within the first hour of delivery and in the first 6 months, and continued breastfeeding until 2 years
Facility level	• Risk factor assessment, including maternal malnutrition, maternal age >35 years, multiple pregnancies, previous PtB, short birth spacing, and substance abuse Regional/tertiary level: • Ultrasonographic cervical length assessment • Foetal fibronectin testing[a] • Inflammatory proteins in maternal serum,[b] amniotic fluid,[b] cervico-vaginal fluid[a] • Biomarker testing[c] • Serum proteomic testing[c] • Genomic DNA testing[c]	• Lower genital tract infection screening and treatment • Screen for maternal infections associated with PtB • Maternal antibiotics for prevention of infection (e.g. pneumonia) associated with PtB • Nutritional supplementation for pregnant women (e.g. zinc for pregnant women or calcium for women with hypertension)[b]	Regional hospital level: • Administer maternal tocolytics to delay delivery until mother reaches health facility with NICU facilities • Administer antepartum glucocorticoids • Low-dose aspirin for preeclampsia prevention • Skilled birth attendants (e.g. midwives) • Family/partner support during labour • Management of preterm labour: treatment with antenatal steroids • Antibiotics to prevent sepsis in PPROM	• Preventive surfactant therapy for preterm neonates • CPAP for respiratory distress syndrome • Management of neonatal infections

Sources: Alfirevic et al., 2017;[58] Bhutta et al., 2014;[56] Jarde et al., 2019;[59] Lamont, 2019;[60] Medley et al., 2018.[57]
CPAP = continuous positive airway pressure; NICU = neonatal intensive care unit; PPROM = preterm premature rupture of membranes.

a Only available in private facilities
b Only for spontaneous preterm birth
c Only in research study settings

Box 1: Priority health interventions recommended to reduce maternal and neonatal mortality, South Africa, 2012 - 2016

Maternal health

- Basic antenatal care (four visits for every pregnant woman, beginning during the first trimester*).
- HIV testing during pregnancy, with initiation of ART and provision of other prevention of mother-to-child transmission (PMTCT) services where indicated.
- Improved access to care during labour through introduction of dedicated obstetric ambulances and establishment of maternity waiting homes (where appropriate).
- Improved intrapartum care (with specific focus on correct use of the partogram, and standard protocols for managing complications).
- Postnatal care within six days of delivery.

Newborn health

- Promotion of early and exclusive breastfeeding, including ensuring that breastfeeding is made as safe as possible for HIV-exposed infants.
- Provision of PMTCT.
- Resuscitation of newborns.
- Care for small/ill newborns according to standardised protocols.
- KMC for stable LBW infants.
- Postnatal visit within six days, which includes newborn care and supporting mothers to practise exclusive breastfeeding.

Community interventions

- Provision of a package of community-based MNCWH services by generalist community health workers working as part of ward-based PHC outreach teams.
- Multi-sectoral action to reduce poverty and inequity, and improve access to basic services, especially improved water and sanitation.
- Development of a MNCWH communication strategy.

*As of 1 April 2017, this has been increased to eight antenatal visits.[61]

Source: NDoH, 2012.[55]

Box 2: Kangaroo mother care: implementation of a key intervention

KMC is a high-yield, low-tech, cost-effective intervention for addressing morbidity and mortality in PtB neonates.[62] Within the public sector, KMC was first initiated in hospitals in KwaZulu-Natal, Gauteng and Mpumalanga provinces.[63] The Western Cape, an early adopter, published its first KMC policy in 2002[64], and updated it in 2011.[65] In 2002, Limpopo Province strengthened its KMC uptake through the Limpopo Initiative for Neonatal Care (LINC).[d] Although KMC is embedded in several MNCWH strategic plans and policies (including the Saving Babies Report 2000,[66] the Tshwane Declaration,[67] the Strategic Plan for MNCWH and Nutrition in South Africa 2012 - 2016,[55] and the National Strategic Plan for a Campaign on Accelerated Reduction of Maternal and Child Mortality in Africa[68]), implementation is uneven within the South African public healthcare system, and no private healthcare facility currently offers KMC, due to the high cost of residential care for mother-baby pairs.

Other factors affecting KMC implementation include lack of equipment and supplies to provide appropriate patient treatment; bottlenecks in leadership and governance; disparate healthcare worker knowledge, skills and attitudes;[69] inadequate planning for neonatal care; inadequate buy-in from some healthcare workers, parents and community members; insufficient time for some caregivers to administer KMC; and misalignment between KMC and some cultural norms.[70]

d Personal communication: Ann-Marie Bergh, University of Pretoria, 1 August 2019.

Conclusions and recommendations

PtB requires a package of interventions targeting prevention, diagnosis and short- and long-term management. While many of these interventions are included in South African policy documents, uptake varies across settings.

The South African Every Newborn Action Plan outlines five strategic objectives to reduce PtB.[71] These include the need to:

- Address barriers to reducing PtB;
- Strengthen best practices for PtB reduction;
- Strengthen accountability at all levels of the health system using regular auditing and reporting processes;
- Identify and include key quality and coverage indicators in the DHIS to assess the impact of interventions; and
- Improve community awareness through campaigns.

In addition to the above, we recommend the following:

- Address the equipment and supplies gap in the public sector by prioritising financial resources for key interventions such as KMC at national and sub-national levels.
- Address leadership and governance challenges that affect quality of care by ensuring buy-in from all key actors, including community leaders and health programme managers. Such buy-in can be strengthened through frequent awareness campaigns on the importance and effectiveness of key neonatal interventions.
- Provide appropriate training, support and supervision for healthcare workers to enable them to address bottlenecks in the system.
- Prioritise the following research areas:
    - Early diagnostic tools/approaches for women at high risk of PtB in the community.
    - Short- and long-term effectiveness of interventions to prevent, predict and manage PtB.
    - Barriers and enablers for the delivery of proven key interventions.
    - Short- and long-term morbidity and mortality associated with PtB, including effect on infants, parents, families and society.
    - Best use of limited resources available to the ELBW population, which constitutes approximately 1% of the newborn population but accounts for 60% of PtB mortality.

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