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REVIEW ARTICLE

A stitch in time: narrative review of interventions to reduce preterm births in Malawi

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Background: The rising rate of preterm births (PTBs) is a global concern, and Malawi has a high rate of PTBs (10.5%). The resulting neonatal and under-5 mortality, morbidity and lifelong disability represent a significant loss of human potential affecting individuals, families and society as a whole. This study aims to review the literature to determine the risk factors for PTB in Malawi and to identify effective interventions to prevent PTBs.

Methods: A literature search yielded 22 studies that were categorized according to risk factors implicated for PTBs and health interventions to reduce the risks.

Results: The study has shown that maternal pregnancy factors, infections, nutrition, anaemia and young maternal age are the main causes and risk factors of PTBs in Malawi. The literature revealed no evidence of community-based interventions for reducing the rates of PTBs in Malawi.

Conclusions: Any successful effort to reduce the rate of PTBs will require a multisector, multilevel strategy targeted at the community, homes and individuals as a package to improve the education, nutrition and reproductive health of girls and women as well as focus on improving the delivery of antenatal services in the community.

Keywords: Malawi, preterm birth, prevention, risk factors

Introduction

Preterm birth (PTB) has emerged as a global and public health priority after the World Health Organization (WHO) published the global rates of PTB. According to the WHO, every year 15 million babies are born before 37 weeks of gestation and PTB is the leading cause of neonatal death and under-5 mortality.[1,2] The International Classification of Diseases 11th revision (ICD-11) defines PTB as 'childbirth before 37 weeks of pregnancy (259 days from the first day of the mother's last menstrual period, or 245 days after fertilization)'.

Based on the gestational age, PTBs are categorized as extremely preterm (<28 weeks [5%]), very preterm (28 to <32 weeks [10%]) and moderate to late preterm (32 to <37 weeks [85%]).[3,4] These categories are relevant for care protocols to improve the survival of babies born at different gestational ages. However, since all preterm babies are at increased risk of morbidity, mortality and lifelong sequelae,[5] this review does not differentiate between the subcategories of PTB.

Malawi is estimated to have a very high PTB rate at 10.5% (uncertainty range 7.4–14.3).[6] In low- and middle-income countries (LMICs) like Malawi, the survival rate for babies born before 28 weeks of gestation is only 10%.[3] Half of the these survivors may suffer neurodevelopmental disorders and long-term health effects such as obesity, hypertension and diabetes.[7] The socio-economic impact includes the individual, their family and society, as the costs include healthcare and loss of human potential and productivity.[8]

Gaps in knowledge

Preterm delivery is the end outcome of the interplay of multiple factors that influence gestational age at birth directly or indirectly, but the complex array and interplay of the risk factors that trigger the pathways early to initiate preterm labour are not well understood.[5] Consequently, research is predominantly concentrated on managing premature labour and newborns rather than

prevention.[5] Even the WHO strategy to end preventable newborn deaths[9] lays out an action plan only to improve PTB outcomes. Unlike high-income countries (HICs), access to appropriate care for better survival is not widely available in low-income countries like Malawi.

Furthermore, multiple studies in HICs have not been able to identify interventions to prevent PTBs, as diagnosis and management of preterm labour is not sufficient to reduce the burden of PTBs.[10] Therapeutic agents and tocolytic drugs have been evaluated to manage preterm labour, but there is no robust evidence to indicate that they can effectively delay PTB beyond 24–48 h after the onset of preterm labour.[11] Progesterone therapy has shown protective benefit only in one-third of pregnancies with a history of preterm labour.[11] Even if these interventions are implemented on a larger scale, the PTB rate would only be lowered by 0.5%.[12]

Finally, there is a paucity of robust evidence that identifies the causes and preventive strategies to reduce PTBs, especially in low-resource settings. Available literature reports different variables and interventions in different contexts.[13] There is no evidence of community-based interventions to address the issue.[14]

In one of the poorest countries in the world with limited resources, the societal and socio-economic impact of the high rate of PTBs presents a persuasive argument to develop effective strategies to prevent and reduce the burden of PTBs. Our analysis is a step forward in this direction.

This review aims to determine the epidemiology of PTB in Malawi and identify population-based risk factors that are amenable to interventions at the individual, family and community levels.

Methods

Setting

According to the Human Development Report 2018,[15] Malawi is one of the least developed countries in the world, ranking 171 out of 189. Total expenditure on health is US$93 per capita and government spending on health is 11.4% of the GDP.[16]

A high incidence of diarrhoea, malaria and human immunodeficiency virus (HIV) and widespread malnutrition account for most of the morbidity and mortality[17] in Malawi. HIV prevalence among adults 15–49 y of age is 9.1%.[18] The *Plasmodium falciparum* parasite prevalence is 15.2%.[19]

The median age at sexual debut for women is 16.8 y compared with 18.5 y for men. The median age of marriage for women is 18.2 y and of first birth is 19.0 y.[20] Interpregnancy intervals are short and half of the births in Malawi occur within 36 months of the preceding birth. Although 97% of women attend at least one antenatal clinic, only 51% record four visits.[20]

Search strategy

On 30 May 2017 and repeated on 18 December 2018, a literature search was performed in Embase, Scopus, Web of Science, MEDLINE, CINAHL and the Cochrane Library. The keywords used were terms related to PTB, Malawi and sub-Saharan Africa (Appendix 1).

Inclusion criteria

Included studies were conducted in Malawi with PTB as a primary outcome and participants were pregnant women regardless of risk factors and comorbid conditions. Randomized controlled trials (RCTs), cross-sectional, case–control, cohort and nested case–control studies evaluating one or more risk factors of PTBs and reporting effect size and qualitative studies incorporating a transparent discussion of the methodology were selected. Studies of unsatisfactory quality using Grading of Recommendations Assessment, Development and Evaluation criteria[21] were excluded, as were studies directed at interventions to manage preterm labour.

The combined database search yielded 1536 articles that were imported into EndNote X8 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, 784 articles were scrutinized by title, keywords and abstract, and 713 were excluded. The full text of 69 eligible articles was read and 22 were selected for the analysis and synthesis (Figure 3).

The data were extracted into an Excel spreadsheet (Microsoft, Redmond, WA, USA) organized by author, date, location, type of study, number of subjects, analysis, risk factors and results. The studies were synthesized and analysed according to the risk factors. Meta-analysis was not done, as the studies had different designs and metrics and evaluated different risks. The study characteristics and findings are presented in appendix tables according to the risk factors identified in the literature review.

A framework for risk factors and interventions to reduce PTBs

The causality of PTB is recognized as being multifactorial,[22,23] but there is no comprehensive framework to identify the risk factors and their interplay in the aetiology of PTBs. Based on the findings from the literature review, we developed a framework based on the categories of risk factors that influence PTB and potential areas for interventions to address the risk factors (Figure 1). Maternal pregnancy conditions and illness as well as behavioural and psychosocial factors are the proximal factors that influence PTBs directly or indirectly, independently or otherwise. For example, Kulmala et al.[24] identified primiparity and malaria as direct and independent risks, and noted their synergistic role in increasing the odds of PTB. The combination of poor nutrition and infection causes anaemia and, along with HIV infection, further increases the risk of PTB.[25] A low body mass index (BMI) and anaemia may be the result of poor nutrition, chronic infection or a combination of both.[26]

Distal risk factors are further removed from the causal pathway and may contribute to the risk of PTB by an interplay of genetic, environmental and sociodemographic influences on maternal conditions. Abrams et al.[27] identified low maternal weight as a risk factor for PTB and noted that it is also associated with undernutrition, poverty and low education, all of which reflect a low socio-economic status (SES). This association between the socio-economic determinants and low maternal weight (proximal risk factor) was also noted by van den Broek et al.[26]

The preventive strategies in the model (Figure 2) are based on evidence from the literature.[8,10,28] The interventions are

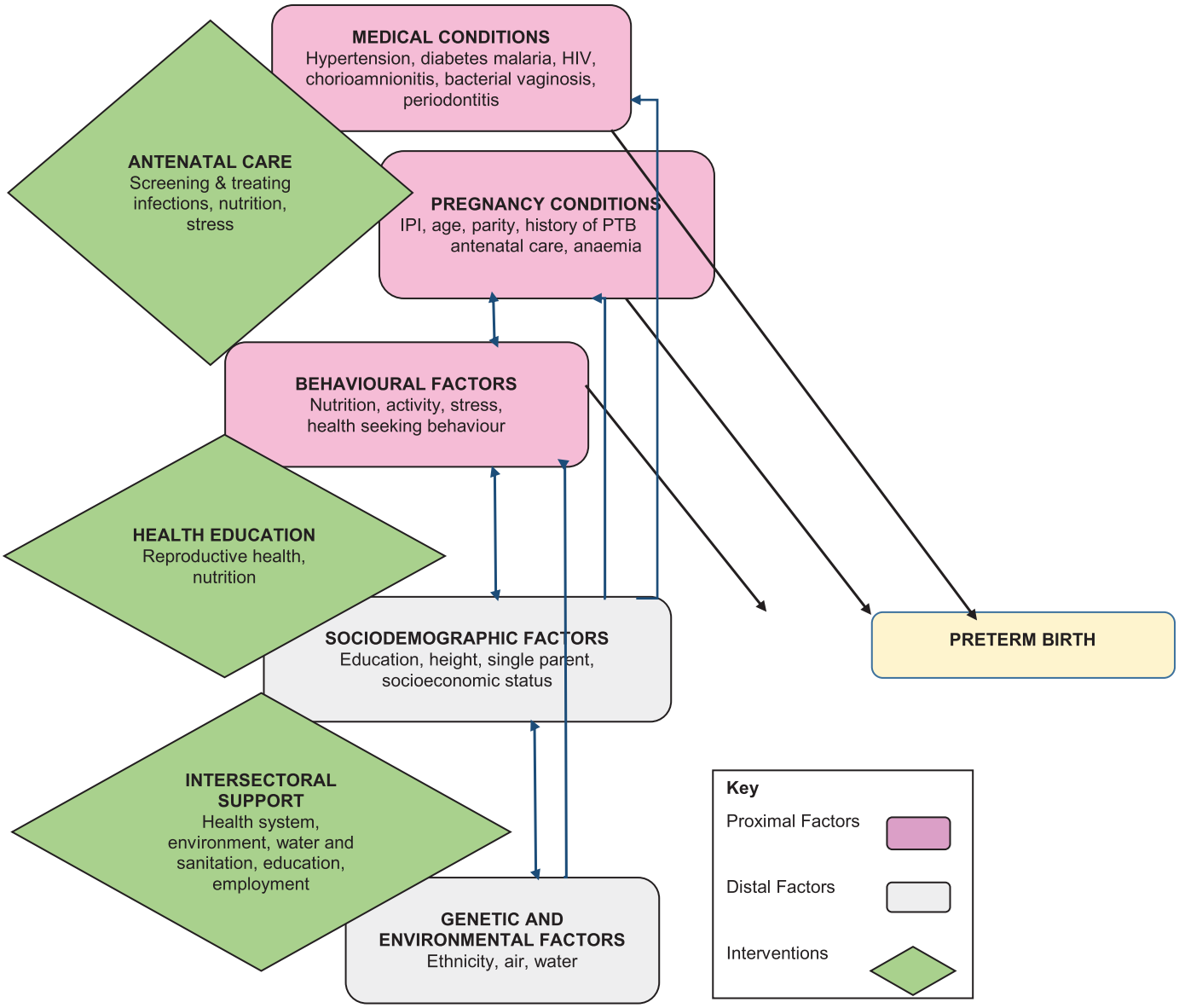

Figure 1. Framework for causes of PTB and interventions to reduce PTBs.

presented according to the known risks at the population level and include health education to modify behaviour; reproductive health before, during and between pregnancies; focused antenatal care (ANC) during pregnancy and social and health system support at the community level. Besides home visits to provide counselling and care during pregnancy, women's groups practising participatory learning and action are a cost-effective strategy to improve outcomes in low-resource settings.[29]

Limitations of the framework

The framework is structured using theory and limited evidence from the literature of associations between different risk factors and the effectiveness of preventive strategies that can be implemented at the community and facility level in Malawi. It does not include the individual-specific risks posed by short cervical length, as cervical cerclage has not been proven to provide any benefit in PTB[14]; progesterone therapy, as the evidence of effect has been demonstrated for only recurrent PTBs in HIC settings[14]; or smoking cessation programmes, as tobacco use is limited in Malawi.[20]

Results

A total of 22 studies were included in this review: 5 cross-sectional, 6 cohort, 6 RCTs or secondary data analysis from an RCT, 1 meta-analysis, 3 qualitative and 1 observational study (Appendix 2).

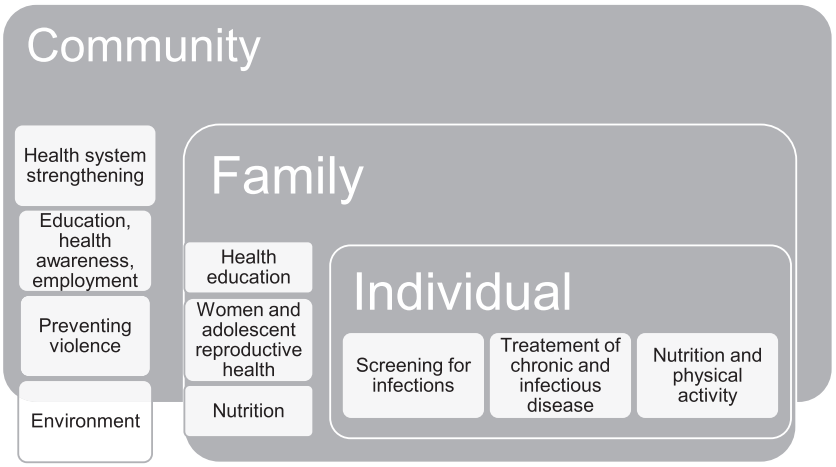

Figure 2. Preventive strategies at the individual, family and community level.

Proximal factors

Maternal pregnancy conditions

Primiparity[24,30] (Appendix 3), history of PTB[24,26] (Appendix 4) and age <20 y[24,26,31,] (Appendix 5) were considered as risks for prematurity. One study[32] documented a reduction in risk for every additional year of age. Abrams et al.[27] found no association between young age and prematurity, which may be explained by the small sample size.

Maternal anaemia was associated with an increased risk of PTB in four studies, and the risk increased with greater severity of anaemia (Appendix 6). Sullivan et al.[33] found no association of anaemia with PTB, possibly because of the small sample size.

One cohort and two cross-sectional studies reported the protective effect of ANC visits on the risk of preterm delivery (Appendix 7).

Maternal medical conditions

The only study on hypertension risk noted that an increase of 5 mm of mean arterial pressure was not associated with preterm delivery[34](Appendix 8).

Six studies analysed HIV as a risk factor (Appendix 9). Four studies[27,32,35,36] reported HIV as a significant risk factor. Kalanda et al.[31] found no association that may be ascribed to the small sample size, or coexisting malaria, which may be an effect modifier. Van den Broek et al.[26] reported no association between HIV infection and PTB, possibly because the samples were tested on completion of the trial and there was no information on antiretroviral therapy (ART) among the participants who declined counselling and testing due to the stigma of HIV diagnosis.

Of the six studies that considered malaria (Appendix 10), only one[27] noted no association with PTB. Persistent parasitaemia[26] and placental and peripheral malaria[24,33] (Appendix 11) were identified as significant risks for PTB. Kalanda et al.[31] noted that taking sulphadoxine–pyrimethamine (SP) once instead of twice increased the odds of PTB.

Chorioamnionitis[27,37] was identified on the pathway to PTB in two studies.

Of the three studies that considered syphilis, only Steketee et al.[30] reported a significant association (Appendix 12). Abrams et al.[27] ascribed the lack of association to a small sample size.

Behavioural and psychosocial factors

Five studies[25–27,30,31] found an association between poor nutritional status and the risk of PTB (Appendix 13).

Distal factors

Of the social and demographic factors, only maternal education was assessed as a risk (Appendix 14). A cross-sectional[32] and a cohort study[33] associated low or no education as a risk for PTB. Single mothers and unwanted pregnancy were not assessed as variables in any study in Malawi. Two studies[31,37] have linked short stature to the risk of PTB (Appendix 15).

Qualitative studies (Appendix 16) established that physical stress and spousal violence were risk factors recognized by community and healthcare personnel in Malawi. Respondents in one study[38] identified cultural influences, dependent decision-making by women, financial considerations and distance to a healthcare facility as barriers to seeking ANC.

Interventions

The studies on interventions to reduce the incidence of PTB in Malawi focused on prophylaxis and treatment of maternal infections (Appendix 17). Marazzi et al.[39] concluded that the administration of triple ART to mothers at 25 weeks gestation was protective and reduced the odds of PTBs by 85%. Chagomerana et al.[40] found mothers who had not received ART had a 2.33 times greater risk of very early PTB and that HIV-positive women who received ART before conception had the lowest risk of PTB.

In an RCT comparing cotrimoxazole treatment prophylaxis (CTP) for malaria in HIV-positive women with SP, Dow et al.[41] observed that the efficacy of CTP for the prevention of malaria and PTB was comparable to that offered by SP prophylaxis.

Prophylactic azithromycin given to women for infections of the reproductive tract did not show a difference in the rates of PTBs

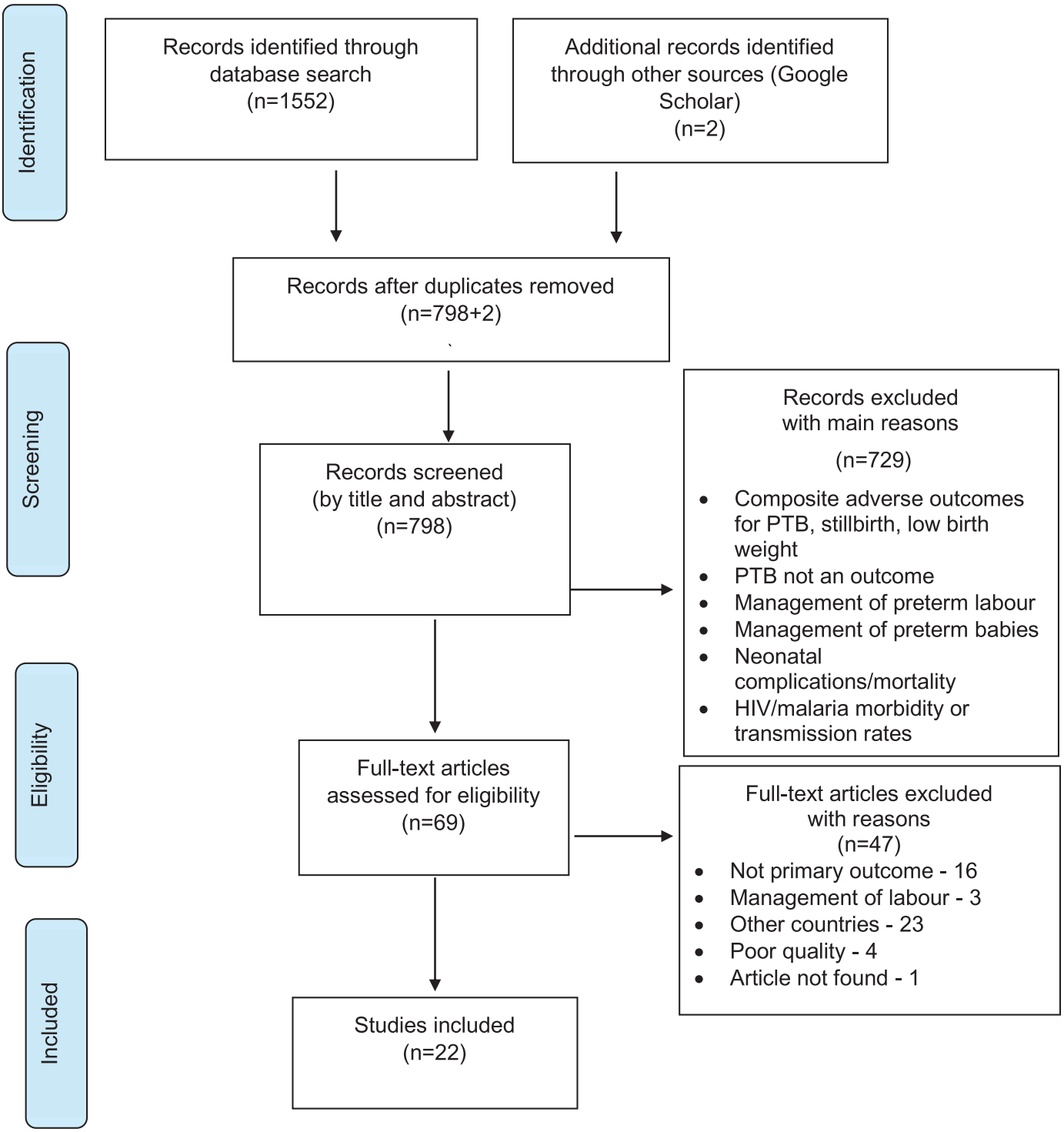

Figure 3. Literature selection flow chart.

in the intervention and control groups in the Azithromycin for the Prevention of Preterm Labor RCT.[42] Luntamo et al.[43] observed a significantly reduced risk of PTB with repeated administration of SP and azithromycin.

Discussion

While no single cause has been identified for the high rate of PTB in Malawi in this review, maternal pregnancy factors, infections, nutrition, anaemia and young age have emerged as the main risk factors of PTB. Interventions to reduce PTB have addressed maternal HIV, malaria and reproductive tract infections, for which the evidence has been ambivalent.

Proximal risk factors

The Born Too Soon Report[10] has identified adolescent pregnancy, short interpregnancy interval and a history of PTB as risk factors for PTB from four studies[14,44–46] and cited weak evidence of risk from maternal anaemia. In Malawi, the median age of first pregnancy is 16.8 y,[20] which carries a 60% higher risk of PTB than in women >20 y of age.[24] The association is also borne out in studies from sub-Saharan Africa (SSA)[47,48] and explained by physiological immaturity, social and economic challenges and behavioural factors. A short interpregnancy interval causing maternal nutritional and physiological depletion is another risk factor relevant in Malawi, where more than half the babies are born within 3 y of the preceding birth.[20] This cohort of young women is amenable to reproductive health interventions at the school and community level to encourage abstinence, later sexual debut and regulated fertility.[28]

While 97% of pregnant mothers in Malawi record at least one ANC visit, only 51% complete four visits as recommended in the WHO model.[20] Cultural beliefs and advice from elders, traditional birth attendants and spiritual healers, and delayed disclosure of pregnancy are all barriers to accessing ANC. Distance, travel costs and better value and benefits in later visits are also important factors for fewer ANC visits overall (earlier visits are often missed).[38] Low attendance and limited monitoring of anaemia, malaria, malaria prophylaxis and nutrition, and low maternal weight compound the risk for PTB. Interventions to strengthen the delivery of high-quality ANC, facilitating regular attendance from the first trimester, provide an opportunity to modify risk factors due to maternal conditions.[49]

Literature from Malawi also associates maternal anaemia with a higher risk of PTB. In a meta-analysis, Haider and Bhutta[50] noted the effect of iron supplementation on PTB in 44 cohort studies, but concluded this was not significant in 48 RCTs (relative risk 0.84 [confidence interval 0.68–1.03]). However, prevention and treatment of anaemia during ANC are effective interventions for preventing stillbirth and low birthweight,[51] and iron supplements are therefore mandatory for ANC.

The role of malaria as a risk for PTB has been established in studies from high transmission areas[24] in Malawi. The protective effect of appropriate malaria prophylaxis, particularly monthly SP, on premature delivery is significant.[43] The regimen could potentially be introduced by monthly visits for ANC or home visits by community health workers.

Apart from in conjunction with antimalarial prophylaxis, there is no evidence for the role of prophylactic antibiotics in preventing maternal infections to reduce PTB in Malawi.[42,52] However, histological evidence of persistence of chorioamnionitis after treatment is indicative of an ineffective antibiotic regimen.[53] This could explain why treatment of infections has not shown an effect on PTB rates despite the evidence of causality.[54,55] Antenatal treatment of specific infections in early pregnancy with appropriate antibiotics may reduce the chemical trigger for preterm labour[42,56] to modify this risk.

Undernutrition and low BMI have been implicated as determinants of PTB in Malawi. However, there is no evidence of a significant effect of protein-energy supplementation on rates of PTB in the literature.[57] Variables such as low SES may be effect modifiers in the association between undernutrition and PTB,[58] and need to be considered when designing a risk reduction strategy.

Distal factors

Low SES and education, environmental and even genetic factors have been implicated as indirect risks for PTB.[59] However, there are no studies to evaluate the impact of education, socioeconomic and environmental influences.

Interventions

There is strong evidence of effect for only two interventions to prevent PTB in HICs: progesterone therapy and smoking cessation.[14] While evidence from HICs cannot be directly translated to low-income settings, this evidence is not useful in the current context for two reasons. First, progesterone therapy is effective in only one-third of women with a history of PTB.[11] Second, the rate of tobacco use in Malawi is <1% among women in the reproductive age group.[20]

The Ministry of Health in Malawi has developed the country's first National Community Health Strategy (NCHS) for the period 2017–2022.[60] The NCHS aims to identify gaps in support for the community health system and resources for an integrated implementation of multiple interventions such as education, employment, water and sanitation, and high-quality service delivery for improved community health outcomes.

There are opportunities to address the multiple risk factors of PTB through these community- and family-oriented interventions designed to affect the entire population of women of childbearing age in a resource-limited country like Malawi. Sensitization of the risks posed by early sexual debut, early marriage and teenage pregnancy through family and community education and access to contraception have the potential to improve PTB rates.[51] Education to improve nutrition and care-seeking behaviour is a strategy that may be effective in modifying the risks of PTB.[61] Finally, better access to ANC with a focus on early attendance, nutritional assessment and management, rigorous screening and treatment for infections and care of maternal conditions is an effective strategy to reduce the burden of PTB. Changing the focus of prenatal care from a strictly medical model to a more comprehensive one that includes social, educational and economic support will further reduce the risk of PTB.

Strengths and limitations

This is the first review exploring the evidence of aetiology and preventive strategies for PTB in Malawi. The review is not systematic and could have missed articles, although the risk of impacts on conclusions is low.

This study found limited data pertinent to the research question, especially for interventions to reduce the incidence of PTB in a low-resource setting. The published studies are mostly based in hospitals or health centres, with heterogeneous populations, risk factors and parameters, which limits the scope of generalization and replicability. Most studies evaluated populations with different characteristics (e.g. malaria or HIV comorbidity) and have not adjusted for confounders (multiple gestation, maternal reproductive tract anomalies and foetal defects) or effect modifiers (infections and SES). While maternal health interventions are documented, there is no available evidence of preconception care or community-based interventions (e.g. supplementation and fortification, cash transfers and incentives, and behaviour change interventions)[62] to reduce PTBs in any country to serve as models for future research in Malawi.

Directions for future research

The main issue for policy planning in Malawi has been the limited data and literature to evaluate causality. There is a need for country-specific high-quality data on the incidence and aetiology of PTBs, including gestational age, multiple or singleton birth, as well as specific maternal parameters, comorbidities and socio-economic information.

Second, the less understood multifactorial causality of PTB poses a unique challenge, particularly in a resource-challenged setting like Malawi. It appears unlikely that a single intervention can reduce the rate of PTBs. Research could include the evaluation of interventions targeting a set of risk factors that is delivered at the community and home level or integrated with the health system and ANC programme at the facility level.

Conclusions

Synthesizing the evidence from Malawi and related studies from other countries, it is clear that PTB is the final outcome of the complex interaction of medical, obstetric, behavioural and social factors. Interventions have addressed only single risk factors, such as infections, nutrition or anaemia, and have had negligible or only moderate effects on outcomes. Interventions to improve maternal nutrition, access to ANC and diagnosis, and treatment of specific infections have the potential to modify most of the identified risk factors and reduce the incidence of PTBs. In addition, the broad range of socio-economic and environmental factors associated with PTBs require measures to address education and adolescent health in socially vulnerable groups to reduce PTBs.

The most beneficial strategy may be a multipronged package of interventions for girls and women from the early and teenage years through to the reproductive years. The broader challenge lies in identifying the most cost-effective mix of strategies at the individual, household, community and facility levels to reduce the risk of PTBs. The strategy will also need to focus on strengthening healthcare delivery, particularly ANC, and building capacity among the scarce healthcare workforce in Malawi in light of limited resources.

Supplementary data

Supplementary data are available at International Health online (http://inthealth.oxfordjournals.org).

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