The overlap between miscarriage and extreme preterm birth in a limited-resource setting on the Thailand-Myanmar border: a population cohort study [version 2; referees: 3 approved with reservations]

Previously titled: Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: A population cohort study

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Abstract

Background: Countries vary on the demarcation gestational age that distinguishes miscarriage and extreme preterm birth (PTB). This study provides a synopsis of the outcome of pregnancy between 22 to <28 weeks’ gestation from a low resource setting.

Methods: A retrospective record review of a refugee and migrant population on the Thailand-Myanmar border with outcome between 22 to <28 weeks’ gestation, was conducted. Outcomes were classified as miscarriage: non-viability prior to 22 week’s gestation with expulsion of products between 22 to <28 weeks’ gestation; or extreme PTB when the fetus was viable at ≥22 weeks and delivered between 22 to <28 weeks’ gestation. Termination of pregnancy and gestational trophoblastic disease were excluded.

Results: From 1995-2015, outcomes occurred between 22 to <28 weeks’ gestation in 0.9% (472/49,931) of pregnancies and 3.8% (18/472) met the exclusion criteria. Most included pregnancies (n=454) had ultrasound done 72.5% (n=329). Overall 43.6% (n=197) were miscarriage and 56.4% (n=257) extreme PTB. Miscarriage (late expulsion) between 22 to <28 weeks was observed with non-viability occurring at an estimated median gestation of 16 weeks. For cases with available data (n=252, 5 missing) the proportion of stillborn was 47.6% (n=120), liveborn 52.4% (n=132); and congenital abnormality 10.5% (24/228, 29 missing). Neonatal death was high 98.5%
Introduction of ultrasound was associated with a 2-times higher odds of classification of outcome as birth rather than miscarriage.

**Conclusion:** In this low resource setting <1% of pregnancy outcomes occur in the 22 to <28 weeks’ gestation window; nearly half were miscarriage; and neonatal mortality approached 100%. In the scale-up to preventable newborns deaths, at least initially, greater benefits will be obtained by focusing on the greater number of viable newborns with a gestation of 28 weeks or more.

**Keywords**

extreme preterm birth, limited-resource, low-income, marginalized, miscarriage, neonatal death, stillbirth, ultrasound

This article is included in the **Mahidol Oxford Tropical Medicine Research Unit (MORU)** gateway.
Introduction

To determine progress towards the Sustainable Developmental Goal (SDG) 3.2 “by 2030, end preventable deaths of newborns and children under 5 years of age”, standardized data collection is critical[1]. It is acknowledged that the lack of universal definitions for miscarriage (abortion), stillbirth and early fetal deaths and live births, and the wide variation in standard of care available for live born extreme preterm births (PTB), affect individual patient care and assessment of SDG progress[1]. Miscarriage remains an awkward condition to define due to variability between and even within countries particularly in relation to laws surrounding termination of pregnancy[2]. There are obvious legal, religious and cultural sensitivities to termination which may inhibit large organizations from specifying an upper limit to define miscarriage[3]. The International Classification of Diseases, provides a graded definition of miscarriage and stillbirth: miscarriage as a pregnancy loss before 22 completed weeks’ gestation; early fetal death: death of a fetus weighing 500 g or more, or aged 22 weeks or more, or with a body length of 25 cm or more; and late fetal death: death of a fetus of 1000 g or more, or aged 28 weeks or more, or with a body length of 35 cm or more[2]. There is still confusion due to overlap in the aforementioned definition. For example, is a stillborn 1000 g fetus with accurately determined gestation born at 27-12 weeks±3 days, a late fetal death because of the birth weight or an early fetal death because of the gestation? For organizations that utilize the WHO definition of stillbirth recommended for global comparison i.e.: “death of a fetus prior to the complete expulsion from the mother at 28 weeks or more of pregnancy” confusion arises with live newborns before 28 weeks. It is difficult to explain to health care workers that stillbirth starts at 28 weeks but live birth can start at <28 weeks.

On the Thailand-Myanmar border at Shoklo Malaria Research Unit (SMRU) the WHO definition of stillbirth with the 28 weeks’ gestation cut point has been used for the past 32 years. Based on this definition there has been a significant decline in stillbirth (28 to 14 per 1,000 live births) and neonatal mortality (49 to 11 per 1,000 livebirths) from 1993–1996 to 2008–2011[4,5]. Miscarriage rates have been stable over time at 10% (2257/23 118) from 1994 to 2013[6]. The outcomes of pregnancies of 28 weeks or more gestation in this area have been published previously and are not the focus of this analysis[7,8,9].

One of the most significant factors in this border region has been the 3 decades long struggle with recurring loss of antimalarials to treat patients with multi-drug resistant *P. falciparum* malaria[10]. The Thailand-Myanmar border was one of the first places in the world to introduce artemisinin-based combination therapy for treatment of malaria in the general population[11]. The artemisinin derivatives were also used initially for treatment of malaria in the 2nd and 3rd trimesters of pregnancy or to save the life of the mother with severe malaria in any trimester[10]. This class of drug distinguished itself in pregnancy as it was first reported by Chinese scientists to cause fetal resorption (or early miscarriage) so it was important to be able to determine gestational age during pregnancy and to have a clear definition of trimester and miscarriage. Quinine remained the WHO recommended drug for women in the first trimester of pregnancy and systematic data collection by local health workers has built an evidence base that has made a significant contribution to global knowledge about antimalarial drug use in pregnancy particularly in the first trimester[11,12].

In the 1990’s at SMRU, gestational age during pregnancy was estimated from fundal height by a formula developed for the study population[13,14] or by LMP, and from late 2001 by ultrasound[5]. In 1995 the only tools available in the field were pregnancy tests, symphysis fundal height measurement (SFH), pinnard and at best (late 1990’s) a small fetal Doppler to detect heart rate which was reserved for use in the delivery room. SFH measurements were routinely carried out at antenatal care and quality control measurement exercises were conducted because it was so heavily relied upon. SFH was examined at every visit until it could be felt for the first time and thereafter approximately every 2–4 weeks unless more frequent repeated measures were indicated. In these circumstances and in the absence of bleeding and not being aware of fetal movements, detection of loss of fetal viability was identified late. When ultrasound was introduced in the area, a first trimester or first ANC visit scan was followed up by a repeat scan initially at 18 weeks and later shifted to 22 weeks. Gestation of the fetus demise could be more readily obtained by ultrasound but for SMRU data to be consistent with the former data, the end of gestation of pregnancy remained constant i.e. as the date of expulsion of the products of conception.
At the same time, work has been standardized for local health workers by use of obstetric guidelines\(^2\). In the guidelines the working definition of miscarriage is outcome of pregnancy before 28 weeks and births (stillbirth and live birth) commence from 28 weeks. This definition has remained unchanged with the establishment of a special care baby unit in this resource limited setting where assisted ventilation of newborns is not available (i.e. birth before 28 weeks is not viable)\(^1\).

The objective of this study is to bring clarity to the nature of the products of conception that are expelled in the 22 to \(<28\) weeks’ gestational age window, highlighting operational issues for low resource settings and the role of ultrasound\(^7\).

**Methods**

**Setting**

SMRU is an operational field-based research unit uniquely combining humanitarian work with research of direct relevance to the local population. It is a limited-resource setting working with marginalized populations on the western border of Thailand in Tak Province. In this area, there are an estimated 140,000 refugees and 200,000 migrants from Myanmar. There have been decades of neglect of the health system in Myanmar and the government is currently trying to address this. The refugee situation on the border of Thailand and Myanmar is amongst the most protracted in Asia but it has set a scenario of how health, particularly among pregnant women and obstetric emergencies of Myanmar people are managed. Due to conflict in Eastern Kayin state, refugees obtained surgical care in Thailand hospitals via a system of referral from Community-Based- and Non-Government Organizations. Health care for migrant pregnant women was established in 1998 by SMRU as there were minimal services available for them (Figure 1).

At SMRU, place and attendance at birth has shifted from 75% occurring at home with traditional birth attendants with no formal training in 1986, to more than 80% of births occurring in health facilities with skilled attendants in 2015\(^11\). SMRU is staffed predominantly by locally trained health care workers for antenatal care and ultrasound\(^6\), child birth\(^13\,22\) and emergencies in adults and neonates\(^10\). Local medics, midwives and nurses do the majority of the clinical work and expatriate doctors assist local staff with 24-hour back up. The eight sonographers undergo a small quality control every 6 months by one of the obstetric doctors. Over 3,000 women register at SMRU antenatal clinics annually and these were well established before birth services were offered. The first birthing unit was opened at Shoklo refugee camp in 1986, with border skirmishes and closure of Shoklo, this was relocated to Maela Refugee camp in 1995, and two more units for marginalized migrant workers were opened in Wang Pha in Dec-2007 and in Maw Ker Thai in April 2010 (Figure 1). The seven signal functions for Basic Emergency Obstetric and Newborn Care, including parenteral administration of an oxytocic, antibiotics and anticonvulsants, removal of retained

![Figure 1. Map of the border area. Location of SMRU clinics where pregnant women can attend for antenatal care and childbirth.](image-url)
products of conception, assisted vaginal birth including breech birth, resuscitation of the newborn using a bag and mask and screened blood transfusions, are provided by local staff. A description of the special care baby unit for neonates has been detailed by Turner et al., but there is no capacity for intubation and assisted ventilation and prohibitive costs limit newborn referrals. Aminophylline is used in place of caffeine for apneas, again due to costs. Local protocols guide care and are regularly updated with trainings on their use by local staff. The protocol for preterm labour recommends dexamethasone (betamethasone is not available) and nifedipine at a gestation of at least 28 weeks. If extreme PTB occurs (<28 weeks) infants are provided with palliative care. Parents are involved and counseled in the process. Women who need caesarean section or who have complex medical conditions are transferred by car to Thai hospitals (45 to 90 minutes away) and these cases require funding.

Pregnancy ultrasound and fetal viability
Ultrasound scans have been performed by local health workers using various scanners, including Toshiba Powervision 7000, Dynamic Imaging (since 2001), Fukuda Denshi UF 4100, and General Electric Voluson-1. Since 2001 all women have been offered two scans: once at booking to determine viability, number of fetus and gestation, regardless of how far progressed the pregnancy is, but preferably between 8 and 14 weeks; and again at 22 (18–24) weeks to reassess viability, measure fetal biometry and major abnormalities and determine placental location. Ultrasound can be repeated at any time as required. For example, if a woman reported absence of fetal movement, or bleeding, or the fundal height did not increase, an ultrasound could be done to determine viability. Measurement of the fetus size at each scan was encouraged. Loss of fetal heart beat could also be an incidental finding when the woman attended for her second scan. Loss of viability with ultrasound could be confirmed by presence of a fetus and absent fetal heartbeat. In some cases, ultrasound confirmed pregnancies persisting to 22 weeks' gestation, but a fetus was never observed, e.g. anovulatory gestation or non-classic gestational trophoblastic disease.

In this setting SFH measurement has been important to determine whether a woman was in the first or second trimester which made the difference between being able to use quinine or artesunate to treat uncomplicated malaria. At antenatal care, pregnant women had abdominal palpation at each visit until the SFH was first palpable and measurable above the symphysis, then SFH was checked monthly up to 32 weeks and weekly from 36 weeks' gestation. In case of doubt, urine (sometimes serum) pregnancy testing was available. It was and still is common to have the SFH measured multiple times in a single pregnancy. Before ultrasound availability, loss of fetal viability could be confirmed by SFH measurements, which were increasing and then levelled off, or decreased, complaints of loss of fetal movement or never feeling movement, bleeding episodes or expulsion of products. Quality control exercises of SFH involved comparing 20 women per month between SFH measurers – a difference of > 1 cm was considered unacceptable and corrections of the firmness of applying the tape measure, correctly placing the end of the tape measure on the upper border of the symphysis pubis and identifying the fundus, were made during these sessions.

Management of fetal loss diverged from high income settings. Before misoprostol was available, induction of pregnancies with confirmed fetal loss was difficult and if there was no vaginal bleeding and the cervix was not open a conservative management style was adopted. Induction with syntocinon, the only available agent for many years, was frequently a prolonged and unsuccessful process. Women were not worried about the loss of the fetal heart beat, indeed there was a chance the pregnancy could be a "dry baby" i.e. fetus papyraceus (considered fortunate in Karen culture) and they were content to wait and see, knowing if there were problems they could come to the clinic. In this low resource context, only surgical emergencies were referred to tertiary hospitals, so non-viable pregnancy loss, with no imminent danger signs did not qualify for referral.

Data extraction and data definitions
All birth records at SMRU are computer based and paper-based records are archived at SMRU head office in Mae Sot. All pregnancy records from 1995 until 2015 in the window period from 22 to <28 weeks' gestation were selected and reviewed case by case by for the present study. The starting point of 1995 was selected, since the first local guidelines for obstetrics was introduced at this time.

For each record the following evaluation was conducted using a step-wise query process:

a) Was there evidence of in utero fetal demise before 22 weeks? If yes, could the gestation of loss be estimated? For example, was fetal anthropometry measured by ultrasound when absence of fetal heart beat was confirmed; or did the SFH measurements stall or decrease (and at how many centimeters) before fetal heart rate could be heard or fetal movements felt, or did the mother report that she never felt fetal movements? Was there evidence that there was never a fetus i.e. that the pregnancy was never viable? Did ultrasound measure only annovulatory pregnancy (blighted ovum)?

b) Was there evidence of in utero fetal viability at 22 to <28 weeks' gestation? If yes, when was the estimated gestation at loss of viability and were there any signs of life at birth?

c) If the outcome was a live birth, what was the neonatal outcome?

Records with evidence of in utero fetal demise before 22 weeks but expulsion between 22 to <28 weeks were classified as miscarriage. Pregnancies with evidence of fetal viability at ≥22 weeks that were expelled between 22 to <28 weeks were classified as extreme PTB (live or stillborn). Gestational trophoblastic disease and termination of pregnancy were excluded. Congenital abnormalities were coded using the ICD-10 criteria.
Statistical analysis

Gestational age was reported by week, for example, 22 weeks included women from 22⁰ to 22+6 weeks, (i.e. 22 weeks plus 6 days) of pregnancy. Continuous normally distributed data, such as gestation and birth weight, were described using the mean, and standard deviation (SD) and compared with the Student’s t-test. Only the first born twin birth weight was retrieved from the electronic files. Non-parametric data, such as gravidity, were described using median and 25th-75th percentiles and compared with the Mann-Whitney U test. Proportions were compared using the Chi-squared test. To assess the role of ultrasound in the final classification as extreme PTB rather than miscarriage between 22 to <28 weeks’ gestation, univariable and multivariable logistic regression was used to determine the association between ultrasound use and outcome, adjusted for first ANC attendance in first trimester and delivering with a skilled attendant (confounders identified a priori). Data was analysed using SPSS version 20 (IBM SPSS, Armonk, NY, USA) and Stata version 13 (StatCorp, College Station, TX, USA).

Ethics statement

Ethical approval for retrospective analysis of pregnancy records was given by the Oxford Tropical Research Ethics Committee (OXTREC 28–09) and after discussion with the local Community Advisory Board (TCAB-4/1/2015)

Results

Between 1995 and 2015, the records of 50,046 women with a known pregnancy outcome were included in the present study. Only a small proportion, 0.2% (115/50,046), of these pregnancies could not be assigned a reliable gestational age (Figure 2). The proportion of all pregnancy outcomes within the gestational window of 22 to <28 weeks, 0.9% (472/49,931) was small and most of these 73.1% (345/472) had an obstetric ultrasound scan and dating.

There were 3.8% (18/372) excluded from analysis: intentional termination of pregnancy involved 13 cases including: six ultrasound confirmed major fetal abnormality (five anencephalic, one holoprosencephaly); two life-threatening maternal conditions both with uncontrollable severe pre-eclampsia; and five self-induced (one of whom was recently widowed); and five gestational trophoblastic disease. The demographic characteristics of the remaining 454 pregnancy outcomes, most of whom had ultrasound, 72.5% (329/454), were summarized (Table 1) as were the numbers and proportions of pregnancy outcome for each gestational age week from 22 to <28 (Table 2). There were 6.2% (28/454) twin pregnancies.

Miscarriage

Of the 454 pregnancy outcomes from 22 to <28 weeks’ gestation 197 (43.5%) were miscarriage (loss of viability before 22 weeks) two of which were twin gestations (23 weeks) (Table 2). More than half of 197 miscarriages occurred at 22 and 23 weeks’ gestation 27.9% (55) and 23.9% (47); with 24, 25, 26, and 27 weeks accounting for 20.8% (41), 10.2% (20), 7.6% (15) and 9.6% (19), respectively.

Loss of viability was not possible to determine for 11 records (nine indicated spontaneous miscarriage and two records could not be assigned a reliable gestational age (Figure 2). The proportion of all pregnancy outcomes within the gestational window of 22 to <28 weeks, 0.9% (472/49,931) was small and most of these 73.1% (345/472) had an obstetric ultrasound scan and dating.

There were 3.8% (18/372) excluded from analysis: intentional termination of pregnancy involved 13 cases including: six ultrasound confirmed major fetal abnormality (five anencephalic, one holoprosencephaly); two life-threatening maternal conditions both with uncontrollable severe pre-eclampsia; and five self-induced (one of whom was recently widowed); and five gestational trophoblastic disease. The demographic characteristics of the remaining 454 pregnancy outcomes, most of whom had ultrasound, 72.5% (329/454), were summarized (Table 1) as were the numbers and proportions of pregnancy outcome for each gestational age week from 22 to <28 (Table 2). There were 6.2% (28/454) twin pregnancies.

<table>
<thead>
<tr>
<th>Registered 1995-2015:</th>
<th>61,829 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown pregnancy outcome 11,783 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>Known pregnancy outcome:</td>
<td>50,046 women</td>
</tr>
<tr>
<td>Pregnancies without estimated gestational age 115 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Delivery or miscarriage:</td>
<td>49,931 women</td>
</tr>
<tr>
<td>Outside gestational age window of interest 49,459 (99.1%)</td>
<td></td>
</tr>
<tr>
<td>Known pregnancy outcomes 22 to &lt;28 weeks:</td>
<td>472 women</td>
</tr>
<tr>
<td>Excluded (termination n=13, gestational trophoblastic disease n=5) (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Known pregnancy outcomes 22 to &lt;28 weeks:</td>
<td>454 women</td>
</tr>
</tbody>
</table>

Figure 2. Study flow. Selection of women in the cohort of 22 to < 28 weeks’ gestation.
Table 1. Baseline demographic characteristics of 454 women with pregnancy outcome 22 to <28 weeks' gestation. *Missing data: weight first ANC, weight less than 40 kg at first ANC n=3; BMI and BMI category n=158; Anemia at first ANC visit n=24. Abbreviation: ANC, antenatal clinic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean [±SD], [min-max]</td>
<td>28 [±8] [13–48]</td>
</tr>
<tr>
<td>Gravidity, median [25th-75th percentile], [min-max]</td>
<td>3 [2–5], [1–15]</td>
</tr>
<tr>
<td>Parity, median [25th-75th percentile], [min-max]</td>
<td>2 [0–4], [0–11]</td>
</tr>
<tr>
<td>Primigravida, % (n)</td>
<td>24.4 (111/454)</td>
</tr>
<tr>
<td>Grandmultipara (more than 4 births), % (n)</td>
<td>16.5 (75/454)</td>
</tr>
<tr>
<td>Weight first ANC, kg, mean [±SD], [min-max] *</td>
<td>48 [±8] [31–81]</td>
</tr>
<tr>
<td>Weight less than 40 kg first ANC, n (%)</td>
<td>8.9 (40/451)</td>
</tr>
<tr>
<td>BMI, kg/m² at first ANC*, mean [±SD] [min-max];</td>
<td>21.5 [±3.3], [13.6–34.2]</td>
</tr>
<tr>
<td>Underweight (&lt;18.5), % (n)</td>
<td>14.2 (42)</td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt; 23), % (n)</td>
<td>61.7 (182)</td>
</tr>
<tr>
<td>Over weight (23 to &lt;27.5), % (n)</td>
<td>18.0 (53)</td>
</tr>
<tr>
<td>Obese (≥27.5), % (n)</td>
<td>6.1 (18)</td>
</tr>
<tr>
<td>Number of ANC visits, median[25th-75th percentile], [min-max]</td>
<td>6 [3-11], [1-22]</td>
</tr>
<tr>
<td>A total of 4 or more ANC visits, % (n)</td>
<td>58.4 (265/454)</td>
</tr>
<tr>
<td>Anemia at first ANC, % (n)*</td>
<td>12.3 (53/430)</td>
</tr>
<tr>
<td>First ANC visit in trimester one (less than 14 weeks), % (n)</td>
<td>55.5 (252/454)</td>
</tr>
</tbody>
</table>

Table 2. Numbers and proportions of pregnancy outcomes by gestational age week 22 to <28 weeks.

<table>
<thead>
<tr>
<th>Weeks' gestation at pregnancy outcome</th>
<th>Total</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>454</td>
<td>71</td>
<td>78</td>
<td>80</td>
<td>60</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>197</td>
<td>(43.6)</td>
<td>55</td>
<td>(77.5)</td>
<td>47</td>
<td>(60.3)</td>
<td>41</td>
</tr>
<tr>
<td>Extreme PTB</td>
<td>257</td>
<td>(56.4)</td>
<td>16</td>
<td>(22.5)</td>
<td>31</td>
<td>(39.7)</td>
<td>39</td>
</tr>
<tr>
<td>Twins†</td>
<td>28</td>
<td>(61.8)</td>
<td>1</td>
<td>(1.4)</td>
<td>5</td>
<td>(6.4)</td>
<td>2</td>
</tr>
<tr>
<td>Extreme PTB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data on live and still birth</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>120/252</td>
<td>(47.6)</td>
<td>12</td>
<td>(75.0)</td>
<td>22</td>
<td>(71.0)</td>
<td>18</td>
</tr>
<tr>
<td>Live birth</td>
<td>132/252</td>
<td>(52.4)</td>
<td>4</td>
<td>(25.0)</td>
<td>9</td>
<td>(29.0)</td>
<td>20</td>
</tr>
<tr>
<td>Survival of Newborns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data NND</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NND day 1</td>
<td>87/131</td>
<td>(66.9)</td>
<td>4</td>
<td>(100.0)</td>
<td>9</td>
<td>(100.0)</td>
<td>17</td>
</tr>
<tr>
<td>NND day 3</td>
<td>114/131</td>
<td>(87.0)</td>
<td>4</td>
<td>(100.0)</td>
<td>9</td>
<td>(100.0)</td>
<td>19</td>
</tr>
<tr>
<td>NND day 28</td>
<td>129/131</td>
<td>(98.5)</td>
<td>4</td>
<td>(100.0)</td>
<td>9</td>
<td>(100.0)</td>
<td>20</td>
</tr>
<tr>
<td>Alive &gt; 1 month</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2*</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise stated; Abbreviations: n.a, NND neonatal death; PTB preterm birth
*Most twins pregnancies were extreme PTB except for 2 which were miscarriage at 23 weeks
†Born alive and probably died but data not available in the record
‡Not sure exact days NND (only 700g and born at home, brought to clinic)
§One died at day 33; one was still alive at 40 months of age
not be located) leaving 186 records. Evidence of fetal demise (absence of fetal heart beat) also known as fetal death in utero, occurred in 60.2% (112/186), with most of these determined by ultrasound (Table 3). The proportion with stalling or decreases in SFH was higher before ultrasound was introduced (Table 3). Extracts demonstrating detection of non-viable pregnancy are provided in Supplementary File 1. Annovulatory pregnancy (blighted ovum) was also a reason for expulsion of products of pregnancy from 22 to < 28 weeks of pregnancy in this setting: 16.8% (19/113) when ultrasound was available (Table 3). In the 112 cases with fetal death in utero the estimated time from non-viability to expulsion was a median of 7^(+/-)IQR 4^+/- to 11^+/- weeks before ultrasound: 6^+ (n=24) vs 7^+IQR 3^+/- to 11^+/- weeks after ultrasound: 6^+ (n=88), p=0.084.

Extreme preterm birth (22 to <28 weeks)
There were 257/454 (56.4%) women with an extreme PTB of which 89.9% (231/257) were singletons and 10.2% (26/257) were twins (Table 2). The gender of the infant was missing for 30.0% (77/257) cases, with the remainder including 56.1% (101/180) males and 43.9% (79/180) females. Amongst the 257 pregnancies ending in extreme PTB, 1.9% (5/257) were missing data on whether the infant was stillborn (Table 2), and for the remaining cases 47.6% (120/252) were recorded as stillbirths (including first born twin), and 52.4% (132/252) were born alive. Most women birthed vaginally, 98.0% (252/257), but there were 1.6% (4/252) delivered by caesarean sections. These four cases were in singleton pregnancies, three at 27 weeks and one at 26 weeks, three of whom had placental pathologies (two placenta praevia and one placental abruption) and one with preterm labour and transverse presentation. These four births all ended in stillbirth with a birth weight available for one case (900g).

The birth weight measured in singletons was not available for 42.0% (108/257) of neonates. Birth weight of 17 congenitally abnormal infants was excluded from analysis. Birth weight in live born, normal singletons in the period before ultrasound (n=18) and when ultrasound was available (n=67) was similar 817±253 (350–1300) and 875±231 (220–1300) g (p=0.380). The means±SD (min-max) birth weight was higher in live born (n=85) than stillborn (n=27) normal singletons infants: 863±253 (350–1300) and 875±231 (220–1300) g (p<0.001). Mean birth weights for singletons and first-born twins were summarized for each gestational age week after excluding birth weight of those with congenital abnormality (Supplementary File 2). Congenital abnormality involved 10.6% (24/227, 30 missing) of extreme PTB and half of these congenital abnormality cases 50.0% (12/24) were stillborn (Table 4).

Newborn survival
Of the 132 liveborn extreme PTB, the fate of one neonate was unknown at one month, of the remaining neonates 98.5% (128/131) had a neonatal death and 1.5% (2/131) survived the first 28 days. The median [IQR, range] age of neonatal deaths was 1 [1–2, 1–28] day, with 87.0% (114/131) by day 3 (Table 2). One newborn died at day 33 and the remaining child survived and was still alive when last seen at 40 months of age, with normal neurodevelopment. The surviving female child was born at 27^+^ weeks, and two ultrasounds, including an early scan at 8 weeks and a later scan at 18 weeks, assured the gestation. The mother was a 32-year-old refugee with a gravidity of two and parity of one, with no history of PTB, who went into spontaneous labour and received a single dose of nifedipine and dexamethasone less than one hour before delivery. Delivery was supervised by skilled birth attendants and after a normal vaginal birth of a 890g baby, the Apgar scores were six and seven, at one and five minutes. The neonate was provided with supportive care (with oxygen delivered by nasal prongs; temperature control, phototherapy, breast milk) because that was all that was available, and discharged home after ten weeks at 1061g.

The role of ultrasound
Use of ultrasound was associated with an increased adjusted(A) OR of classification of outcome as an extreme PTB rather than miscarriage: AOR 2.09 (95%CI 1.31–3.34, p=0.002); while attending in the first trimester for the first antenatal visit and delivery at SMRU clinics were not associated: AOR 1.29 (95%CI 0.87–1.91, p=0.212), and AOR 0.93 (95%CI 0.61–1.45, p=0.802), respectively (Table 5).

**Discussion**
The window of gestation from 22 to <28 weeks involved less than 1% of all pregnancy outcomes and in this low resource setting, 4 in 10 outcomes at this gestation were miscarriage (i.e. the fetus had died before reaching 22 weeks). Close to three-quarters of pregnancies in the cohort had an ultrasound and this was associated with a 2 times higher odds of the outcome being classified as an extreme PTB rather than a miscarriage. This suggests that ultrasound adds clarity to the outcome of pregnancy in this 22 to <28 week window, mostly because it detects the presence of a fetus and the fetal heart beat or in this setting even the presence of annovulatory pregnancy – both of which are not

**Table 4.** Reason for miscarriage classification at 22 to <28 weeks’ gestation and the estimated gestational age of the event (median [min-max] in weeks).

<table>
<thead>
<tr>
<th>Event</th>
<th>Before ultrasound (n=73)</th>
<th>Ultrasound (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>EGA of loss of viability</td>
</tr>
<tr>
<td>Fetal death in utero</td>
<td>24 (32.9)</td>
<td>16^+IQR 11^+ to 21^+</td>
</tr>
<tr>
<td>SFH stalled or decreased</td>
<td>41 (56.2)</td>
<td>16^+IQR 8^+ to 21^+</td>
</tr>
<tr>
<td>Annovulatory</td>
<td>8 (10.9)</td>
<td>8^+IQR 5^+ to 8^+</td>
</tr>
</tbody>
</table>
easily identified with more limited tools (pregnancy test, SFH and pinnard/fetal heart rate Doppler). Use of ultrasound confirmed that more than one-third of outcomes expelled from 22 to <28 weeks’ gestation that were not viable at 22 weeks. Under the ICD 10 definition these could be (wrongly) defined as extreme PTB based on gestation alone, which would falsely inflate stillbirth and extreme PTB perinatal mortality rates.

Amongst the outcomes classified as extreme PTB, nearly one-half were stillborn, 98.5% had a neonatal death of which two-thirds occurred on day one, and there was a high proportion (as expected) of congenital abnormalities 10.6% amongst these newborns. A high congenital abnormality rate is expected amongst this age group in a setting that does not actively screen for abnormalities25. Two infants emerged from the neonatal period, one died at day 33 and one female of 27+5 weeks gestation survived infancy (end of the first year). Not only are the outcomes of pregnancies of 22 to <28 weeks’ gestation in this setting dismal, the proportion of pregnancies that are involved, relative to all pregnancies with a known outcome, is small (0.9%). The 98.5% neonatal deaths in the 22 to <28 weeks’ gestation contrasts sharply to previously reported early premature (defined as 28 to <34 weeks’ gestation) annual deaths at SMRU Maela Refugee Camp, in 2008 to 2011 of 37.9% (11/29), 17.5% (7/40), 22.2% (8/36) and 16.7% (3/18), respectively10. A recent review from a high income setting suggests extremely premature infants and extremely low birth weight infants (<1000g) remain at considerable risk, with a mortality of 30–50% and morbidity of 20–50% in survivors, regardless of technological advances and child health expertise26. It could be argued that if more than palliative care was offered to the newborns at SMRU outcomes may have been different but with no means to provide assisted ventilation improvements would remain marginal. Nearly half of the extreme PTB were stillbirths (47.6% (120/252) again contrasting to the aforementioned 2008 to 2011 cohort in infants of 28 weeks or more with rates per year of 1.0% (15/1528), 1.0% (15/1527), 0.9% (13/1400), and 1.4% (19/1325) respectively10. These different proportions are important because they emphasize that the benefits that can be obtained for greater numbers of more viable newborns, at least initially, in the scale-up to preventable newborn deaths27, is in those of 28 weeks’ gestation or more in low resource settings. Current

### Table 4. Congenital abnormalities, deformations and chromosomal abnormalities in 24 extreme preterm newborns, according to ICD-10 coding. *multiple abnormalities, enalapril exposure; ** also undiagnosed heart murmur.

<table>
<thead>
<tr>
<th>System</th>
<th>Description</th>
<th>ICD-10 code</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Anencephaly</td>
<td>Q00.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Encephalocele*</td>
<td>Q01</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Microcephaly</td>
<td>Q02</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
<td>Q03</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Brain abnormality, unspecified</td>
<td>Q04.9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Spina bifida</td>
<td>Q05</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Malformation of cardiac chambers, not specified</td>
<td>Q20.9</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Oesophageal atresia</td>
<td>Q39</td>
<td>2</td>
</tr>
<tr>
<td>Urinary system</td>
<td>Outflow obstruction</td>
<td>Q64.7</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Talipes (home birth, few details)</td>
<td>Q66.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Phocomelia</td>
<td>Q72.2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>Fetal hydrops Not specified</td>
<td>P56</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Massive cystic hygroma</td>
<td>Q87.8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Severe amniotic bands**</td>
<td>Q79.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Twin to twin transfusion syndrome</td>
<td>Q89.9</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>(suspected) Trisomy-21</td>
<td>Q90</td>
<td>1</td>
</tr>
</tbody>
</table>

*Encephalocele and other abnormalities: arthryogyrophosis, microphthalmia – enalapril exposure

### Table 5. The association between use of ultrasound and outcome classification as extreme PTB or miscarriage between 22 to <28 weeks (n=454). Numbers are % (n), Missing data: Place of birth SMRU (22). *Ultrasonic was not introduced at SMRU until late 2001. Abbreviation: ANC antenatal consultation, SBA skilled birth attendant.

<table>
<thead>
<tr>
<th></th>
<th>Extreme PTB n=257</th>
<th>Miscarriage n=197</th>
<th>Odds Ratio (95% CI), P-value</th>
<th>Adjusted odds ratio (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound*</td>
<td>Yes (all 2002–2015)</td>
<td>62.9 (207/329)</td>
<td>37.1 (122/329)</td>
<td>2.55 (1.67–3.88), p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>No (all 1995–2001)</td>
<td>40.0 (50/125)</td>
<td>60.0 (75/125)</td>
<td></td>
</tr>
<tr>
<td>Early ANC attendance</td>
<td>1st trimester</td>
<td>53.0 (133/251)</td>
<td>47.0 (118/251)</td>
<td>1.39 (0.96–2.03), p = 0.084</td>
</tr>
<tr>
<td></td>
<td>2nd/3rd trimester</td>
<td>61.1 (124/203)</td>
<td>38.9 (79/203)</td>
<td></td>
</tr>
<tr>
<td>Delivery at clinic</td>
<td>Clinic</td>
<td>61.5 (177/287)</td>
<td>38.5 (110/267)</td>
<td>0.74 (0.50–1.12), p = 0.151</td>
</tr>
<tr>
<td></td>
<td>Home</td>
<td>54.5 (79/145)</td>
<td>45.5 (66/145)</td>
<td></td>
</tr>
</tbody>
</table>
resources in HIC offer the possibility of survival for extreme PTB, but this diverges significantly from resources in LMIC. Overall, this data supports the WHO definition of 28 weeks to define birth (live birth and stillbirth), and < 28 weeks a pragmatic definition of miscarriage.

In low resource settings there are many reasons why women may have a late outcome (22 to <28 weeks’ gestation) of a miscarriage (non-viable before 22 weeks) (Table 3). Women seemed prepared to wait or opt for conservative management in the absence of bleeding or pain even when made aware of loss of fetal heart beat. Induction for fetal loss during this window period is associated with higher rates of retained placenta which often require more operative services than what is available at clinic level. In this setting, operative services for the Thailand-Myanmar border have largely been obtained in the border hospitals of Thailand, but most refugees and marginalized migrant do not speak the Thai language. Coming in to the clinic for an induction when there is no pain or bleeding (no obvious problem that is felt by the woman herself) may be perceived as being of greater consequence than not being able to plant or harvest crops, or not being able to receive daily wages which the family depend upon. Information on fetal movement was rarely volunteered so there may be cultural reasons for apparent tolerance to loss of fetal viability and that was clearly documented on some of the antenatal records when the news was revealed of absent fetal heat beat, the woman was not worried because it may mean she could deliver a fetus papyraceus, which, surprisingly, is culturally fortunate. A greater depth of information on the views of fetal loss in this critical window period women from low-income settings is required to provide culturally appropriate services (Supplementary File 1).

Identifying congenital abnormality is one of the recommended measures to reduce stillbirth and neonatal deaths. Within SMRU, rural clinics can provide routine ultrasound by local health workers and SMRU has trained others to provide gestational age assessment, but not screening for anomalies. This is in part due to the additional workload and higher level of skill required. Nevertheless due to viewing a high number of normal pregnancy scans local sonographers recognize gross abnormalities without any additional training. These cases are brought to the attention of the doctor and can be discussed during a counseling session with the parents. Specialist assistance can be obtained by networking internationally for expert feedback on diagnosis and management of certain ultrasound conditions. This has been instrumental to decision making in the SMRU setting. A broader IT based national or international ultrasound consultancy group could be a useful consideration to support the roll out of ultrasound in low resource settings where experts remain in short supply. A further debatable consideration is whether pre-pregnancy identification of congenital abnormalities is helpful for the neonate in low income settings where access to sophisticated care is limited or unaffordable and more importantly services that can help parents with congenital or genetic problems are absent. On the contrary there is argument for identifying in-utero conditions such as hydrocephalus which may save the mothers’ life because mortality or morbidity from obstructed labor or caesarean section complications for an abnormal infant can be prevented by early induction.

The median number of six antenatal consultations (Table 1) is high for pregnancies ending before 28 weeks’ gestation in a limited-resource setting. Ultrasound was routinely available twice for women before 28 weeks’ gestation if they came early enough (50% attended in first trimester) with ultrasound offered at the first antenatal visit, and again at 18–22 weeks. The WHO has recently, for the first time, recommended one ultrasound scan before 24 weeks of gestation as a standard part of antenatal care. In the same document, the basic ANC model, which included four ANC visits recommended in 2002, was finally amended to at least eight ‘contacts’ to improve a woman’s experience of care. SMRU has never used or promoted the ANC basic model of four visits, mostly because only frequent (preferably weekly) contacts were previously shown to reduce maternal death from malaria in an area where chemoprevention was not possible, due to multidrug resistant strains of P. falciparum. A recent review suggests that significant inequality exists not just in the burden of PTB for LMICS compared to HIC but also in the research agenda for progress on PTB prevention. A plethora of publications such as The Lancet Every Newborn series (http://www.thelancet.com/series/everynewborn) and PLoS collections on Maternal Health (http://collections.plos.org/s/maternal-health) have been directed towards improvements needed in LIC on reporting and reducing stillbirth, PTB and neonatal death. The gap between HIC and LIC on issues relating to highly technology screening and prenatal testing of embryonic and fetal tissue are large with many LIC struggling to provide sufficient human resources and clinical services for basic antenatal services and care in childbirth. Registration of births is incomplete in many LIC and dating pregnancies reliably a particularly challenging issue. Registration of births is incomplete in many LIC and dating pregnancies reliably a particularly challenging issue. On the Thailand-Myanmar border, SMRU has integrated basic ultrasound delivered by local sonographers to routine ANC and this has been highly acceptable to women. Efforts have been directed towards having local staff skilled in routine gestational age scanning, standard care at antenatal clinics and at birth, and in newborn care.Record keeping has been based on the cut-off point of 28 weeks’ gestation for birth and miscarriage and while that has been a strength in directing human resources in the delivery room and in special care baby unit to viable neonates it has also resulted in weaker reporting of pregnancy outcomes from 22 to <28 weeks, which is an obvious limitation of this data set. Another limitation of the analysis is the 21 year period of the cohort. This could however be viewed differently as it puts into perspective what a small group of pregnancies are involved: approximately six live born extreme PTBs per year compared to >2,000 births of 28 weeks’ or more per year. While there have been changes over time including the introduction of a special care baby unit and ultrasound, there has been no change in the assisted ventilatory support of newborns, which is not available. In the foreseeable future, improvement of pregnancy outcome from 22 to <28 weeks’ gestation does not appear feasible or affordable. Nevertheless, gestation and viability, best confirmed by ultrasound, are important to establish best practice in
limited-resource settings and to make effective use of affordable and effective interventions, such as basic newborn resuscitation.

In a low resource setting the outcome of pregnancy between 22 to <28 weeks’ gestation involves <1% of all outcomes, a high proportion of miscarriage, with one-in-two of the extreme PTBs being stillborn and amongst livebirths a neonatal mortality approaching 100%. The distinction between miscarriage and extreme PTB in this gestational window is improved by ultrasound but this is unlikely to result in improvement in survival due to significant resource constraints. Pragmatic definitions of viability could assist low resource settings in the scale-up towards reducing preventable newborn deaths and afford greater benefits to newborns more likely to survive with a gestation of 28 weeks or more.

Data availability
Due to ethical and security considerations, the data that supports the findings in this study can be accessed only through the Data Access Committee at Mahidol Oxford Tropical Medicine Research Unit (MORU). The data sharing policy can be found here: http://www.tropmedres.ac/data-sharing. The application form for datasets under the custodianship of MORU Tropical Network can be found in Supplementary File 3.

Author contributions
RM, VC and KM conceived the study. RM, MKP, JW, AMM, VC, KM, SP and FN carried out the research. RM, KM, VC and FN carried out the first draft of the manuscript. MKP, HW and SP contributed to the data design and preparation of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests
No competing interests were disclosed.

Grant information
This work was supported by the Wellcome Trust Thailand Major Overseas Programme 2015–2020 [106698].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments
This research would not have been possible without the staff of SMRU and pregnant women who came to the clinics at this difficult gestation, and we take this opportunity to thank them for their participation.

Supplementary File 1
Extracts of birth records demonstrating identification of non viability.
Click here to access the data.

Supplementary File 2
Mean birth weight of extreme preterm births by gestational age between 22 to <28 weeks.
Click here to access the data.

Supplementary File 3
Application form for data
Click here to access the data.

References

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Open Peer Review

Waldemar A. Carlo
Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, AL, USA

Abstract
The Methods section of the abstract does not distinguish well the classification used. It seems there were two groups but this is not clear from the structure of the sentence. How was non-viability versus viability assessed?

It is stated that non-viability was determined at a median GA of 16 weeks. It is unclear in what cases would non-viability of births at 22-28 weeks can be determined at 16 weeks.

Methods
What was the quality control for data collection? Were clinicians trained in data collection? Were data collectors prospectively assessing the quality of the data? What QI efforts were made to improve data collection?

Were the definitions of stillbirth versus neonatal death prospectively applied throughout the whole period of data collection? What signs of live birth were assessed? How was HR assessed?

What resuscitation measures used in HR was not audible? Were data systematically collected on bag and mask ventilation, incubator use, IV fluids, oxygen supplementation, etc?

Results
The outcome of 19% of booked pregnancies was not known. This is an important problem as pregnancies losses may be over-represented in these unknown outcome pregnancies.

The stillbirth rate is very high especially at the lower gestations. For example, over 40% of births at up 26 weeks were assessed to be stillbirths. There is a frequent of limited assessment for live birth at the lowest gestations. It is common to assess that a newborn is stillbirth because resuscitation is not implemented when few signs of live birth are present. Signs of live birth are not reported. Resuscitation efforts are not reported.

It is concerning that birth weight was not available for 42% of the births? Other basic data also were frequently not available. This raises concerns about the quality of the data.

Gestational age may be underestimated as one SD is above 1000 g which is unlikely for a population of 22-27 week pregnancies.
Data on provision of care are not provided well. It is unclear to what extent live births were provided full support (other than the therapies stated not to be available).

**Discussion**
In the Discussion, the authors appear to implicate that palliative care was generally provided. Details on this should be provided in Results.

The Discussion does not address most major limitations including the 19% of the pregnancies without outcome data, the post-natal interventions rate of use, and the rate of provision of palliative care.

The Discussion is lengthy and yet does not address critical aspects of the limitations so the study can be put in a better perspective and better interpret its contribution to the literature.

**Is the work clearly and accurately presented and does it cite the current literature?**
Partly

**Is the study design appropriate and is the work technically sound?**
No

**Are sufficient details of methods and analysis provided to allow replication by others?**
No

**If applicable, is the statistical analysis and its interpretation appropriate?**
Yes

**Are all the source data underlying the results available to ensure full reproducibility?**
No

**Are the conclusions drawn adequately supported by the results?**
No

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Nov 2018
Rose McGready, Shoklo Malaria Research Unit, Thailand

Referee Report Version 2
01 Aug 2018 Waldemar A. Carlo, Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, AL, USA
Approved with Reservations

We would genuinely like to thank the reviewer Dr Waldemar A Carlo for his repeated review and acceptance to take time to understand this manuscript. The comments have helped to clarify the contents and limitations of the manuscript. A point – by – point response to each comment (in bold
Abstract
1. The Methods section of the abstract does not distinguish well the classification used. It seems there were two groups but this is not clear from the structure of the sentence. How was non-viability versus viability assessed?
Amendments to abstract significant to correct this.

2. It is stated that non-viability was determined at a median GA of 16 weeks. It is unclear in what cases would non-viability of births at 22-28 weeks can be determined at 16 weeks. The sentence “Miscarriage (late expulsion) between 22 to <28 weeks was observed with non-viability occurring at an estimated median gestation of 16 weeks.” … says miscarriage – not birth: and has now been amended
“Individual patient analysis of all miscarriages, estimated non-viability to have occurred at a median of 16 weeks despite late expulsion between 22 to <28 weeks.”
Details are provided in the methods but the space limitation of the abstract prevents further elucidation of the reviewers’ query scenario e.g.
A woman may present for the first time at 6 months (24 weeks GA) by LMP, she is sure of her dates but the ultrasound shows absent FHB in a fetus with a FL of 16 weeks (the HC may or may not be possible to obtain depending on why the fetus is so small) e.g FDIU since 16 weeks or IUGR only growing to a 16 week size. The expulsion occurs from 22 to <28 weeks pregnant based on LMP.

Methods
3. What was the quality control for data collection?
The records have been quality controlled for data entry since 1986 when the antenatal care program commenced, firstly by author FN and later by RM. The data has been quality controlled for completeness and correctness of entry as this has been the most intensely studied population (dataset) in terms of malaria in pregnancy worldwide. Gestational age has been a significant issue for decades as antimalarial drug exposures and pregnancy outcomes have been so important in this population where P. falciparum drug resistance is amongst the highest in the world. In addition significant efforts with gestational age were important to understand the association of artemisinin derivatives (the backbone of antimalarial treatment worldwide today) with fetal resorption.

4. Were clinicians trained in data collection?
Yes

5. Were data collectors prospectively assessing the quality of the data?
Yes

6. What QI efforts were made to improve data collection?
Amendment at methods: section of data extraction

7. Were the definitions of stillbirth versus neonatal death prospectively applied throughout the whole period of data collection?
Yes. See supplementary file 1 for clarification. The introduction has also been modified to conform with the reviewers’ suggestion.

8. What signs of live birth were assessed?
In clinic based birth heart rate was assessed. In clinic and home births respiratory effort, and movement were assessed (or asked to the birth attendant).

9. How was HR assessed?
Auscultation
Auscultation

10. What resuscitation measures used in HR was not audible?
< 28 weeks none. This is not without reason in our experience: while the baby may live it does not live for very long as no accessory support can be provided.
≥ 28 weeks: 5 inflation breaths and then action dependent on HR according to the neonatal drill which is published elsewhere (Janet S et al. PLoS One 2018, 13:e0190419 which is ref 45 in v2.0).
Clarified in the methods, in section “Setting”, last paragraph.

11. Were data systematically collected on bag and mask ventilation, incubator use, IV fluids, oxygen supplementation, etc?
Yes, these data were systematically collected. We have clarified the text as follows:
“If extreme PTB occurs (<28 weeks) infants are provided with palliative care. Parents are involved and counseled in the process. No resuscitative efforts were offered to live born infants of 22 to <28 weeks’ gestation as no further sophisticated care i.e. intubation, incubators, surfactant, parenteral nutrition etc. was available, unlike infants of ≥28 weeks’ gestation.”[ref 45 in v2.0]
The two references Turner and Janet (both open access) are important as they describe everything that does happen (e.g. bag and mask ventilation etc) when an infant is of 28 weeks’ gestation or more, in this low resource environment.

Results

12. The outcome of 19% of booked pregnancies was not known. This is an important problem as pregnancies losses may be over-represented in these unknown outcome pregnancies.

We agree with the reviewer and we have added
- Amendment to the first sentence of the results (and abstract).
- This limitation of the data as the first paragraph to the discussion.

However we do not think that this limitation detracts from our main conclusion i.e. the need to focus on viable fetuses that have reached a GA of 28 weeks.

13. The stillbirth rate is very high especially at the lower gestations. For example, over 40% of births at up 26 weeks were assessed to be stillbirths. There is a frequent of limited assessment for live birth at the lowest gestations. It is common to assess that a newborn is stillbirth because resuscitation is not implemented when few signs of live birth are present.

Thank you and this has been added as a limitation.
- the reviewers comment (Before the section on palliative care…)
- to further explain the high rate of stillbirth as many of these births would have been by emergency C-section in a HIC setting, not vaginal birth. (After the section on palliative care…)

Signs of live birth are not reported.
Amended, see methods, data extraction and data definitions; 2nd bullet point.

Resuscitation efforts are not reported.
See point 11.

14. It is concerning that birth weight was not available for 42% of the births? Other basic data also were frequently not available. This raises concerns about the quality of the data.

We agree this is a limitation. As the 28 week cut-point has been used to define birth and miscarriage it has been an ongoing process to motivate staff to weigh infants born prior to this
gestation. Parents also see no reason to bring a stillborn or perinatal death infant to the clinic for a weight.

15. **Gestational age may be underestimated as one SD is above 1000 g which is unlikely for a population of 22-27 week pregnancies.**

There are no SD above 1000g, only the upper range. These are possible from the local centiles produced for this population from ultrasound dated pregnancies (Rijken MJ et al. (2014) Quantifying Low Birth Weight, Preterm Birth and Small-for-Gestational-Age Effects of Malaria in Pregnancy: A Population Cohort Study. PLoS ONE 9(7): e100247. doi:10.1371/journal.pone.0100247). They may represent incorrect EGA but birthweight give lower stillbirth rates than gestational age cut-offs and this has been added to the discussion.

14. **Data on provision of care are not provided well. It is unclear to what extent live births were provided full support (other than the therapies stated not to be available).**

Amended. This is the same as point 9. There was no resuscitation, intubation, incubators, surfactant, parenteral nutrition etc.

**Discussion**

15. **In the Discussion, the authors appear to implicate that palliative care was generally provided. Details on this should be provided in Results.**

Amended as same as point 12.

16. **The Discussion does not address most major limitations including the 19% of the pregnancies without outcome data, the post-natal interventions rate of use, and the rate of provision of palliative care.**

Amended as same as point 11 and 13.

Limitations are addressed in paragraph 1, paragraph 3.

In paragraph

17. **The Discussion is lengthy and yet does not address critical aspects of the limitations so the study can be pit in a better perspective and better interpret its contribution to the literature.**

Agree: Significantly reduced

**Competing Interests:** I have no competing interests.
Thank you for the opportunity of reviewing this manuscript entitled “Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a population cohort study.” The work done is impressive and has the potential to provide insight in how we: (a) view and manage the ‘grey zone’ in low resource setting, (b) support mothers and their families who present for care when in this ‘grey zone’, and (c) should allocate the limited resources in reducing neonatal mortality in low resource setting.

Title
The title is very long and needs to be shortened. Moreover, it needs to better capture the findings of the study.

Abstract
Introduction: Clearly define WHO and study definitions – this is critical to understanding the study results. Objective: Associations were also examined (page 4) which is not captured here. Methods: a more comprehensive description is required. Results: please share the statistics related to the association found. Conclusion: bold and very relevant!

Article Content:

Introduction
The definition of stillbirth, miscarriage, preterm birth, and neonatal death has been identified as problematic given overlaps in gestational cut-points. Hence, it is imperative that these terms be defined at the outset so that there is conceptual clarity both with respect to variables being examined and the intended purpose of the study. This would also help with interpretation of findings.

There are discrepancies with respect to the definition of miscarriage in the introduction and methodology (e.g., bottom of page 4). Moreover, issues are highlighted about accuracy of gestational assessment, lack of ultrasound diagnosis of congenital abnormality which further impacts definitions of terms particularly with inclusion of data before 2001. It is therefore not clear what the study hopes to accomplish by examining pregnancy outcomes between 24 to < 28 weeks’ gestational age over a 20 year period.

The second paragraph: the information pertaining to preterm births, neonatal deaths, and rationale for the high rates seems misplaced. Explain the relevance of the information shared to the aims of the study. Furthermore, explain the consequence(s) of poor reporting of stillbirth and neonatal deaths.

The third paragraph: relevance of statistics related to mortality secondary to malaria is not clear.

The introduction should more clearly articulate the conceptual approach (i.e., operationalize definitions), explain the rationale of the study, and situate information related to preterm birth, neonatal deaths, maternal mortality within the context of study aims.

Methodology
Data extraction and data definition
Data were reviewed from 1995 to 2015 which is problematic as care patterns have changed significantly in this time frame (details shared in second and third paragraph). For example, the authors explain that there has been a shift from home birth to hospital births and improvement in care during the antenatal period. These changes are likely to reduce fetal mortality, as well as maternal and neonatal mortality. Thus, it is not clear why this time span was used for the purpose of this study. Moreover, ultrasound was introduced in 2001 which means that accurate assessment of gestational age may be an issue prior to
this time. Ultrasound has also changed the way in which loss of fetal viability was confirmed (e.g., fundal height measurements). Given the intent to describe viability and mortality in the window of 24 to <28 weeks’ gestational age it is important to have consistency in the way definitions are operationalized throughout the course of the study.

Data Quality – birth records are computer based; however is initial data recorded on paper and then transferred to the computer system? Please comment on the accuracy of data and strategies employed in ensuring quality data. Based on the results it appears that there are potential issues with data quality as in 4.4% of the 204 pregnancies between 24 and < 28 weeks’ gestational age there was missing data; birth weight data was available for 57.6% of neonates. This is a limitation and your discussion should explain how this impacts interpretation of findings.

Ultrasound assessment – was this done by one person? If multiple assessors please comment on inter-rater reliability of ultrasound dating.

Page 4 – please indicate the actual average of transporting women by car to the Thai hospital. Is this a potential limitation of the study?

**Statistical analysis**

“Univariable and multivariable logistic regression was used to assess the association between estimation of gestational age by ultrasound, homebirth and year of birth, and birth outcome (birth rather than miscarriage).” A better description needs to be provided about the analytic plan and how it relates to the objectives of the study. The analytic plan should identify how variable were identified to be important to include in the multivariable logistic regression analysis. How were variables entered in the multivariable logistic regression analysis? Explain the rationale for the decision(s). It appears that the outcome of interest is birth however only 57.8% of these were live birth. What outcome was used? Furthermore, only one infant survived. What is the minimal sample size required for your multivariable regression analysis?

**Results**

Pregnancy outcomes were unknown for 19.1% of the registered women – what was the issue? Only 50.6% of the women had their first antenatal care visit in trimester one which has implications for accuracy of gestational dating using ultrasound (most accurate in the first trimester).

The inclusion of termination of pregnancy is confusing particularly since two were for maternal conditions at 24 and < 28 weeks’ gestation which in high income countries would be managed by inducing labour.

Table 1 – Characteristic age, years – please indicate what the data represents (as you do for other variables).

Figure 2 – study flow diagram can be expanded to more clearly display outcomes including stillbirths, live births, and survival.

Figure 3 – Can be removed as I don't think it provides any additional information.

**Discussion**

The results do not demonstrate the bias detailed in the opening paragraph. Is there an opportunity here to compare historical cohorts (before introduction of ultrasound and after introduction of ultrasound)?

**Competing Interests:** No competing interests were disclosed.
I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Halit Pinar
Warren Alpert Medical School, Brown University, Providence, RI, USA

The study titled ‘Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a population cohort study’ is a well thought out and interesting study and has a lot of potential to be better and more useful to the reader.

The following are some points I am hoping will be useful in the authors’ efforts to improve the manuscript.

**Recommendation 1:**

The main objectives of the study are not clear. If it is challenging the definition (or lack thereof) of the miscarriages and its overlap with extreme premature deliveries, please say so more clearly. Obviously, this overlap is very confusing and just to demonstrate the conceptual difficulties one faces when trying to analyze a data set like this, is a worthy cause.

Spend more time with these conceptual inconsistencies so the readers who are not familiar with these concepts will have a better understanding of your objectives and results.

**Recommendation 2:**

Third paragraph in the Introduction:

The background information given is interesting but very short. In addition, it is not clear what purpose it serves in the general context of the manuscript. Recommendation: It would be ideal to provide more detailed information that is pertinent to the etiology of maternal diseases, miscarriages, stillbirth etc. in that region to help the reader to better understand the characteristics of the patient population.

**Recommendation 3:**

It appears there is a discrepancy between the definition of miscarriages at the end of the first paragraph of page 4 and the definition given under the header of miscarriage in the second column.

The first definition: When a fetus dies <24 weeks but is delivered between 24-28 weeks.

The second definition is used in the first sentence just under the subtitle of ‘miscarriage’: 114 women out of 318 women miscarried from 24-28 weeks’ gestation and the distribution is given according to the gestational age. In this section it appears that for a fetus to be called he/she does not have to die<24 weeks and be delivered after 28 weeks. In addition, in our experience it not very common for the mother to keep the dead fetus for two or more weeks (in this case up to 4 weeks).
Recommendation 4:

Second column on page 6. The correct term for ‘surface’ examination is ‘external’ examination.

Recommendation 5:

I would recommend exclusion of terminations. That adds more confusion to the calculations and it is considered a very different group.

Question 1:

The true consequence of using different GA for the definition of fetal death/stillborn vs miscarriage (except causing confusion) is not clear.

Question 2:

Since you have the numbers, what happens if you analyze the data where a pregnancy loss up to 20 weeks gestational age will be classified as a miscarriage and any delivery ≥20 weeks is classified either as a liveborn or stillborn?

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Jul 2018

Rose McGready, Shoklo Malaria Research Unit, Thailand

Halit Pinar, Warren Alpert Medical School, Brown University, Providence, RI, USA

Approved with Reservations

The study titled ‘Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a population cohort study’ is a well thought out and interesting study and has a lot of potential to be better and more useful to the reader.

Agree with potential to be better.

The following are some points I am hoping will be useful in the authors ‘efforts to improve the manuscript.

Recommendation 1:

The main objectives of the study are not clear. If it is challenging the definition (or lack thereof) of the miscarriages and its overlap with extreme premature deliveries, please say so more clearly. Obviously, this overlap is very confusing and just to demonstrate the conceptual difficulties one faces when trying to analyze a data set like this, is a worthy cause.

Thank you for your patience with the manuscript – we are trying to articulate i.e. that this window (22 to <28 weeks) can include miscarriage, a large proportion.
Spend more time with these conceptual inconsistencies so the readers who are not familiar with these concepts will have a better understanding of your objectives and results.

We agree that we did not succeed to give clarity on the main objective. We have rephrased the entire manuscript. The aim of this study is to contribute to the sparse body of evidence from limited resource settings that support the use of the 28 weeks’ gestational age cut-point for stillbirth. We also argue for the usefulness of <28 weeks’ gestational age to define miscarriage.

**Recommendation 2:**
**Third paragraph in the Introduction:**
The background information given is interesting but very short. In addition, it is not clear what purpose it serves in the general context of the manuscript. Recommendation: It would be ideal to provide more detailed information that is pertinent to the etiology of maternal diseases, miscarriages, stillbirth etc. in that region to help the reader to better understand the characteristics of the patient population.

Thank you for this comment – the introduction has been rewritten to address this point and Recommendation 1.

**Recommendation 3:**
It appears there is a discrepancy between the definition of miscarriages at the end of the first paragraph of page 4 and the definition given under the header of miscarriage in the second column.

The first definition: When a fetus dies <24 weeks but is delivered between 24-28 weeks.
The second definition is used in the first sentence just under the subtitle of ‘miscarriage’: 114 women out of 318 women miscarried from 24<28 weeks’ gestation and the distribution is given according to the gestational age. In this section it appears that for a fetus to be called he/she does not have to die<24 weeks and be delivered after 28 weeks.
The definitions have been laid out more clearly. For this analysis the definitions of miscarriage is absence of viability before 22 weeks but delivery in the 22 to <28 week window and extreme preterm birth is presence of viability and delivery at 22 to <28 weeks.

In addition, in our experience it not very common for the mother to keep the dead fetus for two or more weeks (in this case up to 4 weeks).
This is a very helpful comment and it is exactly what we want to highlight for an in issue relevant to low resource settings. We have an average of 6 weeks before expulsion.
We suspect this must be a source of confusion in other low resource settings as these types of pregnancy outcomes are hard to document without a reliable method of measuring pregnancy viability e.g. ultrasound or multiple.
We are also trying to highlight that the experience in low resource settings may not match the bulk of published evidence available.

**Recommendation 4:**
**Second column on page 6.** The correct term for ‘surface’ examination is ‘external’ examination.
Amended as suggested

**Recommendation 5:**
I would recommend exclusion of terminations. That adds more confusion to the
calculations and it is considered a very different group.
Amended as suggested

Question 1:
The true consequence of using different GA for the definition of fetal death/stillborn vs miscarriage (except causing confusion) is not clear.
We have spent more time to explain this in the introduction.
The practice of obstetrics in resource limited settings is not as efficient. Miscarriage can occur at 22-28 weeks (the window of extreme preterm birth) and in the setting described in this manuscript where significant effort has been placed on assessment of gestational age, we present data to prove that point. The WHO definition of 28 week cut-point that defines a stillbirth is attractive and pragmatic for low resource settings.

Question 2:
Since you have the numbers, what happens if you analyze the data where a pregnancy loss up to 20 weeks gestational age will be classified as a miscarriage and any delivery $\geq$20 weeks is classified either as a liveborn or stillborn?
We have gone back to the records to classify outcomes from 22 to $<28$ weeks gestation as miscarriage, livebirth, stillbirth, neonatal mortality. The records of 20 and 21 weeks start to have too much missing data to contribute reliably to the argument.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above. Competing Interests: No competing interests were disclosed.

Competing Interests: No competing interests were disclosed.