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Simplified management protocol for term neonates after prolonged rupture of membranes in a setting with high rates of neonatal sepsis and mortality: a quality improvement study

Diana Olita'a,[1] Roland Barnabas,[1] Gamini Vali Boma,[1] Wendy Pameh,[2] John Vince,[2] Trevor Duke[2,3]

[1]Department of Paediatrics, Port Moresby General Hospital, Port Moresby, Papua New Guinea
[2]School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea
[3]Centre for International Child Health, Royal Children's Hospital, University of Melbourne, MCRI, Parkville, Victoria, Australia

Correspondence to
Prof Trevor Duke, Centre for International Child Health, Royal Children's Hospital, University of Melbourne, Parkville VIC 3052, Australia;
trevor.duke@rch.org.au

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ABSTRACT

In low-income and middle-income countries, courses of antibiotics are routinely given to term newborns whose mothers had prolonged rupture of membranes (PROM). Rational antibiotic use is vital given rising rates of antimicrobial resistance and potential adverse effects of antibiotic exposure in newborns. However missing cases of sepsis can be life-threatening.This is a quality improvement evaluation of a protocol for minimal or no antibiotics in term babies born after PROM in Papua New Guinea. Asymptomatic, term babies born to women with PROM >12 hours prior to birth were given a stat dose of antibiotics, or no antibiotics if the mother had received intrapartum antibiotics, reviewed and discharged at 48–72 hours with follow-up. Clinical signs of sepsis within the first week and the neonatal period were assessed. Of 170 newborns whose mothers had PROM, 133 were assessed at 7 days: signs of sepsis occurred in 10 babies (7.5%; 95% CI 4.4% to 13.2%) in the first week. Five had isolated fever, four had skin pustules and one had fever with periumbilical erythema. An additional four (3%) had any sign of sepsis between 8 and 28 days. There was one case of bacteraemia and no deaths. 37 were lost to follow-up, but hospital records did not identify any subsequent admissions for infection. A rate of sepsis was documented that was comparable with other studies in low-income countries. This protocol may reduce antimicrobial resistance and consequences of antibiotic exposure in newborns, provided safeguards are in place to monitor for signs of sepsis.

INTRODUCTION

In low-income and middle-income countries, courses of antibiotics are routinely given to term newborns whose mothers have prolonged rupture of membranes (PROM), but this may be unnecessary and expose many newborns to the adverse effects of antibiotics. In Papua New Guinea (PNG), a low-middle-income country, neonatal mortality is high, approximately 28 per 1000 live births, and neonatal sepsis is a major cause. In 15 PNG hospitals in 2017, 61% (4057) of 6681 newborn admissions to special care nurseries were for infection.[1] The case fatality rate for neonatal sepsis treated in hospitals in PNG is 6%–7%.[1 2] As in many low-income countries, in PNG there are rising rates of antimicrobial resistance in hospitals and communities, multiresistant organisms contribute to high mortality from neonatal sepsis, and bacteriology services are limited.[3–5]

PROM is defined as the rupture of amniotic membranes 12–18 hours or more prior to delivery of the baby, and is a common cause of hospital admission and antibiotic use.[6 7] Babies born to mothers who have had PROM are at risk of early-onset neonatal sepsis (EONS).[8 9] Rupture of membranes is also classified as preterm (<37 weeks' gestation) or term. PROM complicates approximately 8%–10% of all pregnancies, and 60% of PROM occurs at term.[10] In a multicentre study in high-income countries, the rates of neonatal infection after PROM was 2.6%,[9] but in low-income countries rates as high as 17% are reported.[11] In PNG, an interval of more than 12 hours rupture of membranes prior to delivery is considered as PROM, and the infant is routinely admitted to the neonatal ward and treated with antibiotics.[12]

Neonatal sepsis is classified as early-onset (EONS, within the first 72 hours) and late-onset neonatal sepsis (LONS, beyond 72 hours).[13] Risk factors for infection include PROM, chorioamnionitis, maternal fever during labour, urinary tract infection and group B streptococcus colonisation.[14] The risk of EONS is greatest when PROM is associated with chorioamnionitis,[15] and in premature and low birthweight babies, and the risk increases with duration of ruptured membranes.[6 16] In addition to colonisation or infection occurring from PROM or during birth, LONS can also be caused by organisms acquired from the caregiving environment, including healthcare-related infections. At least up to 7 days, there is much overlap in the mechanisms of acquisition of infection in EONS and LONS.[13]

Neonatal infections include pneumonia from aspiration of infected amniotic fluid or infected blood or meconium at the time of birth, bacteraemia, and skin, eye or umbilical cord infection. Some babies may show signs of infection at birth or within a few hours after delivery, and others may show signs of sepsis 24–72 hours after delivery. Clinical signs suggesting infection include temperature instability, respiratory distress, vomiting, abdominal distension, poor feeding, lethargy or irritability, hypotension, tachycardia, pallor, petechiae, cyanosis and jaundice.[17]

Antibiotics (penicillin or erythromycin) given to mothers with preterm PROM delays delivery and

reduces infections in mothers and their infants[16 18]; however, the management of term infants born after PROM varies greatly.[17] A 2004 Cochrane review concluded that there was insufficient evidence to support the use of prophylactic antibiotics in well term infants born after PROM and other maternal risk factors for neonatal infection, and that more clinical studies were needed.[17]

The use of prophylactic antibiotics may result in unnecessary treatment of newborns who would not have developed an infection, and may result in complications such as antibiotic resistance, ototoxicity from aminoglycosides, disruption of the normal development of gut microbiota, increased susceptibility to Gram-negative and fungal infections, and increased risk of wheezing in infancy.[11 13 19–22] Other adverse effects include impairment of breast feeding and exposure to nosocomial infections from prolonged hospital stay. On the other hand, missing cases of serious bacterial infection in newborns can be life-threatening, and in low-income countries the ability to monitor babies for signs of sepsis is limited. In addition to the direct potential effects of antibiotics on the newborn, we identified the problem of large numbers of neonates being admitted to the neonatal unit or mothers being hospitalised for 5 days so that their newborns could receive antibiotics for PROM. This contributed to overcrowding, and often separation of babies from their mothers.

We conducted this quality improvement study to evaluate the safety and effectiveness of a protocol based on giving minimal or no antibiotics to well term babies born after PROM and its effect on neonatal sepsis.

METHODS

Location and intervention design

This is a prospective quality improvement study at Port Moresby General Hospital (PMGH) in PNG. PMGH is a tertiary referral hospital which serves all areas of the country, but sees a large number of patients from the National Capital District and nearby Central and Gulf provinces. The hospital has approximately 15 000 women delivering each year.

Participants

We enrolled term newborns whose mothers had PROM more than 12 hours before delivery, whether prelabour or intrapartum. We included infants delivered via normal vaginal delivery, caesarean section or assisted instrumental delivery, with good Apgar scores (>7 at 1 min), birth weight of 2 kg or more, and with no clinical signs of sepsis at birth.

Newborns were excluded if their mothers had preterm rupture of membranes, they were born before arrival at hospital, preterm delivery (<37 weeks' gestation), weight less than 2 kg or had clinical signs of sepsis.

Simplified management approach

The management protocol was different for infants whose mothers had received intrapartum antibiotics and those whose mothers had not. This was because of the possibility that different risks would exist, that is, that receipt of antibiotics by mothers in labour would have mitigated the infection risk in the newborn. Newborns whose mothers had not received intrapartum antibiotics were given a stat dose of amoxicillin 30 mg/kg and gentamycin 5 mg/kg administered intramuscularly. Newborns whose mothers had received intrapartum antibiotics received no antibiotics.

Follow-up and assessment

Newborns were screened for clinical signs of sepsis at 12–24 hours and 36–48 hours after birth and discharged from the hospital at 48 hours if they remained well. If PROM exceeded 48 hours, mothers and their babies were observed for 72 hours before discharge. If babies developed clinical signs of sepsis at any of the screening time points, cultures were taken of blood and other possible sites of infection, and antibiotics were started. The following clinical features recommended by WHO as indicating neonatal sepsis were used to assess for sepsis in the infants: reduced feeding ability, no spontaneous movement, fever (temperature ≥37.5°C), hypothermia (temperature <35.5°C), severe chest indrawing, fast breathing (respiratory rate >60/min), convulsions, any jaundice in the first 24 hours and deep jaundice at any age (yellow palms and soles). Other clinical features for local sepsis were also checked, including purulent eye discharge, skin pustules, and purulent discharge or erythema surrounding the umbilical cord stump.[23]

After discharge, the infants were reviewed between 6 and 8 days and assessed for clinical signs of sepsis. Mothers were advised at the time of discharge on the signs of sepsis and when to return for review. These signs included very hot body, cold skin of the arms and legs, inability to suck or feed well, inactive or too sleepy, fast breathing, chest and ribs pulled in when breathing, abnormal movement or stiffening of limbs, and yellow discolouration of palms and soles. Other signs included skin pustules, purulent eye discharge and purulent discharge from the cord. If any of these signs were present at any time after discharge, mothers were advised to bring their babies immediately to the nursery or postnatal ward for review. Mothers were also advised on breast feeding and good hygiene practices to reduce the risk of infections. If infants had any signs of sepsis after discharge, they were admitted for appropriate investigations and treatment with antibiotics. The majority of mothers had mobile phones and used public transport services. Mothers were given a number to call if they had concerns regarding their babies.

Outcome measures

The primary outcome was the development of neonatal sepsis within 7 days. This was defined as suspected clinically based on clinical signs, or confirmed with blood culture or cultures from other possible sites of infection. Sepsis included any *one or more* signs of cord infection, skin sepsis, ophthalmia neonatorum, pneumonia, urinary tract infection, bacteraemia and meningitis. The diagnoses were based on the presence of *one or more* of the features of sepsis indicated by WHO, or localising clinical features such as cord, skin or eye infection, cerebrospinal fluid (CSF) inflammatory response, or positive blood, urine or CSF culture.[23]

The secondary outcomes included admission to the special care nursery or the paediatric general ward with neonatal sepsis, and neonatal deaths.

Data collection and analyses

Data collection included information on maternal characteristics: antenatal, intrapartum and delivery details; neonatal characteristics; follow-up details; and ascertainment and documentation of any signs of sepsis using standard criteria.

Data were entered in a Microsoft Excel spreadsheet, and analysed using AcaStat V.2200 and Stata V.14 statistical software. Continuous variables were described as median (IQR) for non-normally distributed data. Categorical variables were summarised as numbers, proportions or percentages. For

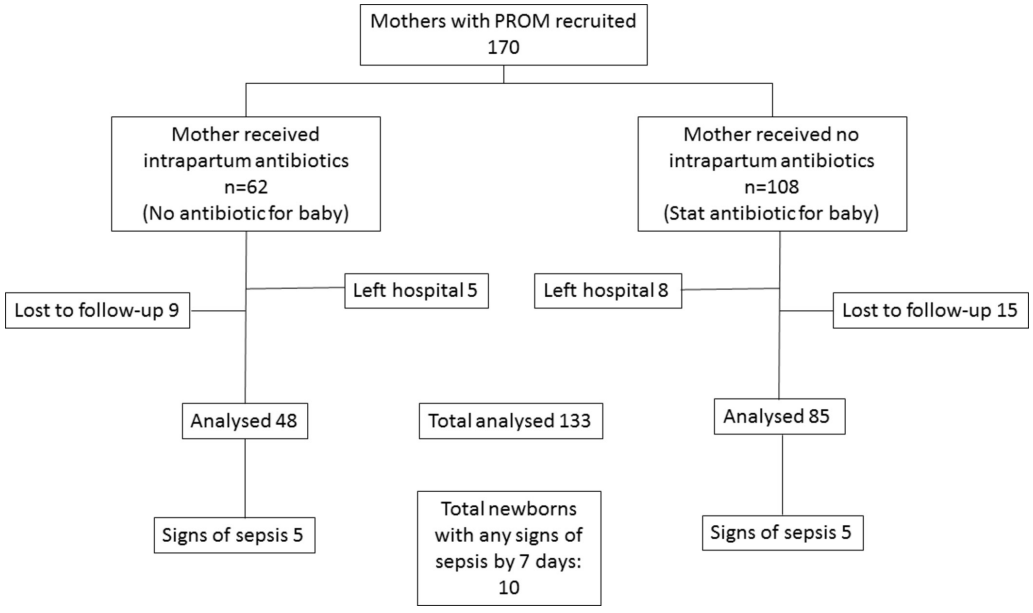

Figure 1 Progression of newborns through the study. PROM, prolonged rupture of membranes.

identifying whether there were statistically significant differences between groups, for continuous variables the Wilcoxon rank-sum test was used for non-normally distributed data. For comparison of proportions, the χ^2 test and Fisher's exact test, where numbers were small, were applied. A level of statistical significance was accepted as 0.05.

RESULTS

A total of 170 neonates were recruited between August 2016 and May 2017. Figure 1 shows the flow of patients in the study. Sixty-two received no antibiotics (because the mothers received intrapartum antibiotics) and 108 were given a single dose of antibiotics (because the mothers had not received intrapartum antibiotics).

Of the 62 mothers who received no antibiotics, 5 absconded and 9 were lost to follow-up, leaving a total of 48 for final analysis. Of the 108 who received stat antibiotics, 8 absconded and 15 were lost to follow-up, leaving 85 for final analysis. A total of 133 mothers and neonates were analysed.

Maternal characteristics

Of the 133 mothers, 48 (36%) had received intrapartum antibiotics and 85 (64%) had not. The median age of the mothers was 24 years (IQR 21.5–28 years). They all lived within the urban and settlement areas in and around Port Moresby. One hundred and twenty-nine (97%) of the mothers had attended at least one antenatal clinic. Seventy-six (58%) of the mothers were primigravidae. For those who were not primigravidae, 22.4% had a history of PROM (n=15/67). Two mothers were HIV-positive and were being treated with antiretroviral treatment during pregnancy. Five mothers had tested syphilis-positive and were fully treated in the antenatal period. Three were found to have pre-eclampsia on admission to labour ward and one had anaemia.

The median gestational age was 39 weeks (IQR 38–40 weeks). The majority of deliveries were vaginal (n=100; 75.2%). The mean duration of rupture of membranes was 21 hours (IQR 16–29 hours) and labour was 18 hours (IQR 11–27 hours). Spontaneous rupture of membranes occurred in 79% of the mothers (n=105). Labour was induced in 31 (23.3%) and augmented in 63 (47.4%) of the deliveries.

Meconium staining of liquor was present in 15% (n=20). Six mothers (4.5%) had signs of chorioamnionitis at delivery (n=6), being maternal fever in two cases and offensive liquor in four cases.

Neonatal characteristics

Of the 133 newborns, 68 (51%) were male. The median Apgar score was 9 (IQR 8–9) at 1 min and 10 (IQR 10–10) at 5 min. The median birth weight of the babies was 3.14 kg (2.88–3.50 kg).

Seventy-one per cent of the babies were discharged at 48 hours (n=96), and the remainder by 72 hours. Sixty-nine per cent (n=87) were reviewed on day 7. Review was delayed by 2–3 days for a few mothers due to financial and transport constraints.

Outcomes

Table 1 describes the primary and secondary outcome measures, and table 2 outlines the characteristics of the babies who

Table 1 Primary and secondary outcomes of the study

Outcomes	Total newborns n=133 (%)	No antibiotics to neonate (mother had received intrapartum antibiotics) n=48 (%)	Stat antibiotics to neonate only n=85 (%)
Primary outcome			
Any clinical sign of sepsis in the first 7 days	10 (7.5)	5 (10.4)	5 (5.9)
Time when clinical signs of sepsis was evident			
Within 24 hours	1 (0.8)	0	1 (1.2)
24–48 hours	3 (2.3)	1 (2.1)	2 (2.4)
48–72 hours	2 (1.5)	1 (2.1)	1 (1.2)
72 hours–7 days	4 (3.0)	3 (6.3)	1 (1.2)
Secondary outcomes			
Any sign of sepsis developed 8–28 days	4 (3)	2 (4.2)	2 (2.4)
Deaths	0	0	0

Table 2 Comparison of characteristics of neonates with and without any sign of sepsis in the first 7 days of life

Variable	Sepsis n=10	No sepsis n=123	P values
Maternal age, median (IQR)	23 (22–27)	24. (21–28)	0.58
Primigravida, n (%)	6 (67)	70 (57)	0.99
Mode of delivery, n (%)			
Normal vaginal	7 (70)	93 (75.6)	0.94
Caesarean section	2 (20)	19 (15.5)	0.98
Instrumentation	1 (10)	11 (8.9)	0.99
Spontaneous rupture of membranes, n (%)	7 (70)	98 (79.7)	0.71
Duration of PROM, median hours (IQR)	18 (16.3–25.5)	21.4 (16–29)	0.31
Maternal antibiotics before delivery, n (%)	5 (50)	43 (35)	0.34
Type of antibiotic given to mother, n (%)			
Single drug	3 (60)	13 (30.2)	0.20
Combination	2 (40)	30 (69.8)	0.99
Labour-induced, n (%)	5 (50)	26 (21.1)	0.04
Length of labour, median hours (IQR)	25.8 (15.1–41.2)	17.4 (10.9–26.0)	0.13
Maternal signs of chorioamnionitis, n (%)	1 (10)	5 (4.1)	0.76
Meconium exposure, n (%)	1 (10)	19 (15.5)	0.99
Newborn weight (kg), median (IQR)	3.48 (3.10–3.68)	3.11 (2.85–3.5)	0.10
Sex, n (%)			0.99
Male	5 (50)	63 (51.2)	
Female	5 (50)	60 (48.8)	
Apgar score, median (IQR)			
1 min	8 (8–8.3)	9 (8–9)	0.01
5 min	10 (10–10)	10 (10–10)	0.30

PROM, prolonged rupture of membranes.

developed any sign of sepsis and those who did not. Ten out of the 133 babies developed sepsis within 7 days (7.5%; 95% CI 4.4% to 13.2%). Of these, six developed signs of sepsis within 72 hours after birth (giving a rate of EONS of 4.5%) and four developed signs of sepsis on days 4–7. Of the 10, 5 were from the no antibiotics group and 5 from the stat antibiotics group (OR for sepsis if given a stat dose of antibiotics 0.54; 95% CI 0.15 to 2.0, p=0.34). Five had isolated fever, four had skin pustules, and one had fever and periumbilical redness as their clinical signs of sepsis.

Using the protocol, 43 babies (32.3%) did not receive any antibiotics and 80 babies (60.2%) had no further requirement for antibiotics beyond a stat dose given as part of the protocol.

Blood culture was positive in two of the cases of EONS. The isolates were a fully sensitive *Moraxella* species and coagulase-negative *Staphylococcus* (the latter a probable contaminant). Two infants were admitted to special care nursery: one for intravenous antibiotic administration after the *Moraxella* culture result was known and another at 4 days of age for phototherapy.

Signs of sepsis between beyond 72 hours of age and within 7 days occurred in 3% of newborns in the study (n=4/133). The four cases were skin pustules identified on day 7 of review. One of these four was from the stat antibiotics group and three from the no antibiotics group. Three of the cases had a positive culture of *Staphylococcus aureus* from the pus swab, all of which were sensitive to flucloxacillin. One was admitted to special care nursery for intravenous antibiotics as the degree of skin sepsis was considered severe. The other three cases were treated with oral flucloxacillin. All infants with signs of sepsis in the first 7 days improved with no complications encountered.

Secondary outcomes

Four additional neonates developed clinical signs of sepsis after 7 days. Of these, two were from the stat antibiotics group and two from the no antibiotics group. They were admitted on day of life 9, 10, 21 and 27. Two were admitted for skin sepsis. Both had *S. aureus* isolated on the pus swab, which was sensitive to flucloxacillin. The other two were admitted with fever but no focus of infection apparent. Both were treated with empirical antibiotics. Blood cultures from all four infants were negative, and they improved and were discharged after completion of treatment. Some of these infections may have been postnatally acquired. There were no deaths of neonates or mothers involved in the study.

DISCUSSION

Evidence-based protocols that appropriately restrict the use of antibiotics are vital to reduce the rising rates of antibiotic resistance. This quality improvement study showed that with the protocol used, the rate of any signs of suspected or proven sepsis in the first week of life in this study was 7.5%: 10 babies out of a total of 133 developed any clinical signs of sepsis. Using the protocol 32.3% of babies (n=43/133) did not receive antibiotics and they did well with no development of clinical signs of infection; 60.2% of babies (n=80/133) received only stat doses of antibiotics and remained well in the first week of life.

Reported rates of neonatal sepsis after PROM vary widely in low-income and middle-income countries, depending on the clinical case definition, the population, the environmental and health service contexts, and the treatment approach (table 3). The few studies conducted have only evaluated EONS, not sepsis in the first week of life, or throughout the neonatal period as our study did. A study from South Africa reported an EONS rate of 17.6% with a definition of PROM >24 hours.[11] In Jordan, using a definition of PROM ≥18 hours, the sepsis rate was 15% overall: lower in babies with prenatal antibiotics use (4.4%) than in those without prenatal antibiotics exposure (21%).[24] In Pakistan, using a definition of PROM >18 hours, the incidence of culture-proven EONS was 4%, but this did not include newborns with only clinical signs of sepsis and negative cultures as we did in our study.[7] Other studies that have combined term and preterm PROM have found incidence rates of neonatal sepsis of 5.5% in Iran,[25] and in Nigeria the rate of chorioamnionitis was 28% and the perinatal mortality rate was 520 per 1000.[26] In our study, the overall incidence of any sign of sepsis was 7.5% in the first week of life, and 10% overall for the neonatal period, but most of these cases were mild and easily treated, and there were no deaths.

There are adverse consequences of unnecessary antibiotic exposure in the newborn period in addition to contributing to the development of antibiotic resistance. Antibiotics in the first few weeks of life affects colonisation of the neonatal intestine, and can lead to the removal of commensal flora and the colonisation with Gram-negative and fungal species.[11 20–22] Treatment with antibiotics in the neonatal period is also an independent risk factor for wheezing that required treatment with inhaled corticosteroids during the first year of life.[14] Therefore giving antibiotics to asymptomatic newborn babies who may not actually have an infection may cause more harm than good.

Table 3 Previous studies of PROM indicating incidence of neonatal sepsis

Study	Country and setting	Definition of term PROM	Cases of term PROM enrolled (n)	Definition of neonatal sepsis	Cases of neonatal sepsis (n)	Incidence (%)	Antibiotics given routinely
Seaward *et al*[9]	Canada, UK, Australia, Israel, Sweden, Denmark.	Rupture at any time prior to onset of labour.	5028	Definite—bacteriologically confirmed infection. Probable—clinical signs of infection plus neutrophilia, neutropaenia, high immature to total neutrophil ratio, or other lab evidence of sepsis.	133 (definite or probable)	2.6	For probable or definite infection, but not specified whether antibiotic prophylaxis was given to all PROM as defined.
Wolf and Olinsky[11]	Johannesburg, South Africa, Transvaal Memorial Hospital for Children.	Rupture that lasted longer than 24 hours before delivery.	51 total: 20 preterm, 31 term	Bacteriologically confirmed infection. Clinical signs of infection.	8 (6 had positive blood cultures and 2 had clinical signs of infection)	17.6 (EONS)	Infants randomly assigned to treatment group with penicillin and kanamycin for 7 days or non-treatment group in the study (not specified whether prophylactic antibiotics were given routinely).
Alam *et al*[7]	Pakistan, Aga Khan University Hospital, Karachi.	Rupture lasting more than 18 hours.	428, term babies n=307; 72%	Culture-positive EONS.	17	4 (EONS)	Not specified whether prophylactic antibiotics were routinely given.
Jackson *et al*[15]	Texas, USA, Parkland Memorial Hospital Newborn Nursery.	Rupture lasting 18 hours or more.	206 (not specified how many term babies)	Positive blood culture and/or clinical signs of infection.	5 (clinical signs of infection)	2.4 (EONS)	For those with neonatal sepsis whether culture-positive or had clinical signs, they received >4 days of intravenous antibiotics. For asymptomatic infants they received stat dose intramuscular penicillin G.
Al-Qaqa and Al-Awaysheh[24]	Jordan, Queen Alia Military Hospital, Paediatric and Neonatology Hospital.	Rupture at least 18 hours.	225 (85 term, 38%)	Positive blood culture associated with two positive CRP readings.	35 (10 in those whose mothers received antibiotics and 25 in those whose mothers did not receive)	15 (EONS)	All received intravenous antibiotics (ampicillin and amikacin) for 3–4 days, then continued Augmentin until culture result was known. Intravenous antibiotics continued for those who showed clinical or laboratory evidence of sepsis.

CRP, C reactive protein; EONS, early-onset neonatal sepsis; PROM, prolonged rupture of membranes.

PROM complicates at least 8% of term births; therefore, in our large hospital where there are 15 000 deliveries a year, up to 1200 newborns would be treated with a 5-day course of antibiotics. Based on this quality improvement study, about 125 would develop some signs of sepsis and require antibiotics in the first month of life. The implementation of this protocol would potentially avoid antibiotic exposure for over 1000 infants and save more than 2100 bed days annually. Contexts—even within a country—are diverse, and this study was done in a periurban setting with health centre and hospital access. In a rural context there will be fewer infants and mothers to follow up, so on one hand may be easier. However in PNG over half of all births occur outside health facilities, and the results of this protocol are not necessarily generalisable to infants born before arrival to a health facility.

There are some limitations to the study. The sample size was relatively small, and a number of babies were lost to follow-up. We report the prevalence of infection not including those lost to follow-up to be conservative in estimates. We carefully reviewed hospital records and did not identify any further presentations of the participating infants. However the number lost to follow-up represents difficulties with the implementation of such protocols in settings where there are many obstacles to children accessing timely care.

There was no control group or background information on the previous sepsis rate in neonates born after PROM and treated according to the standard management of 5 days of antibiotics, so no direct comparison was made; however, the incidence rate of 7.5% is in the middle of the range of the few observational studies of EONS described in table 3. We used a very low threshold for identifying neonatal sepsis, and even with that only 10.5% of babies had any sign of sepsis in the first month of life.

CONCLUSION

In a resource-limited country with high rates of bacterial sepsis and neonatal mortality, there was a rate of possible sepsis of 7.5% among term babies born after PROM using the simplified management approach with few or no antibiotics in the first week of life. Using this protocol nearly 90% of babies had reduced antibiotic exposure, potentially avoiding many complications.

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Contributors DO, TD, GVB and RB designed the study, supervised by the other authors. DO recruited the patients and collected the data. DO and TD analysed the data. DO wrote the first draft of the manuscript with input from TD and JV. Subsequent drafts were reviewed and revised by all authors.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the University of Papua New Guinea School of Medicine and Health Sciences Medical Research Ethics Committee. The study was carefully explained to all mothers who were eligible, and informed consent for participation was gained before enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note Dr Wendy Pameh passed away after this study was completed.

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