STRENGTHENING ANTIBIOTICS STEWARDSHIP AT MOWBRAY MATERNITY – NEONATAL UNIT

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ABBREVIATION

ASP	Antibiotics Stewardship Program.
AWaRE	Access, Watch and Reserve
BC	Blood culture
CAI	Community-acquired infection.
CONS	*Coagulase-negative Staphylococcus*
CRP	C – reactive protein
DAAD	Deutscher Akademischer Austauschdienst (German Academic exchange services)
E.coli	*Escherichia coli*
EML	Essential Medicine List
EMLc	Essential medicine list for children
GBS	*Group B Streptococcus*
HAI	Hospital-acquired infection
HCWs	Health care workers
HH	Hand Hygiene
MMH	Mowbray Maternity Hospital
NICU	Neonatal intensive care unit
PPS	Point prevalence survey
SOP	Standard operating procedures
VLBW	Very low birth weight
WHO	World Health Organisation

Definition of terms

Extreme preterm premature	baby born <28 gestational weeks.
Very preterm	Premature baby born 28 – <32 gestational weeks.
Moderate to late preterm	premature babies born between 32 – 37 completed weeks.
Term	a baby born after 37 completed weeks of gestation.
VLBW	a baby born weighing less than 1500gm.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Antibiotics are the most prescribed medication in Neonatal Intensive Care Units (NICUs), especially for the treatment of early-onset sepsis. The most prescribed drug is Ampicillin, used on average in up to 97% of patients in the NICU [1].

Antibiotics may be lifesaving for truly infected infants, but prolonged antibiotic therapy may alter a preterm infant's microbiome. It has been shown to negatively influence immunological, endocrine, and neural pathways and play an essential role in development [2-4]. Prolonged antibiotic therapy in preterm infants without proven infection has been associated with the development of necrotising enterocolitis (NEC). It has been shown to increase the risk of mortality, bronchopulmonary dysplasia, retinopathy of prematurity, and periventricular white matter damage and also has contributed to the course of multidrug resistance in NICUs [5-7].

In March 2017, the World Health Organization (WHO) – Essential Medicines List (EML) working group classified antibiotics in the EML for Children (EMLC) into Access, Watch, and Reserve. The "Access" group generally contains narrow-spectrum antibiotics recommended as the first and second choice for most common clinical infection syndromes, such as penicillin, gentamycin and Cephalosporins. The "Watch" group contains a broader spectrum of antibiotic classes corresponding to the highest priority agents on the list of critically important antimicrobial drugs for human medicine, e.g., Meropenem. The "Reserve" group consists of last-resort antibiotics for targeted use in multidrug-resistant infections such as Colistin. These groups are collectively known as the "AWaRe" classification. This classification can be used to analyse and categorise the use of antibiotics in a facility [8].

Burden of sepsis

Neonatal sepsis is the third most common cause of death for children under five years. In 2015, Sub-Saharan Africa accounted for half the 400 000 global deaths caused by neonatal sepsis and 66% of these sepsis deaths occurred within the first 24 hours of life, four times the deaths caused by HIV and 1.6 times more than deaths due to malaria [8, 9].

In South Africa, the prevalence of neonatal sepsis is around 12% [8]. The main causative organisms for early-onset sepsis are *Group B streptococci* (GBS) and occasionally, *Listeria monocytogenes.* Hospital-acquired infection (HAI) or late-onset sepsis is mainly gram-negative sepsis. Known causative organisms for HAI include *Escherichia coli, Coagulase–negative Staphylococci (CONS), Staphylococcus aureus, Enterococci, Klebsiella species, Enterobacter species, Pseudomonas species, Salmonella species, Haemophilus influenza, Neisseria meningitis, Streptococcus pneumoniae* and *Acinetobacter baumannii* [9-12].

Although the incidence of culture-proven sepsis is declining worldwide [9], antibiotic use for culture-negative sepsis in the absence of a positive blood culture has remained between 6 to 16-fold more than for confirmed sepsis [13]. A study done in South Africa showed the rate of positivity in blood cultures is around 8.5%, while empirical antibiotics use was 46.7%, indicating overtreatment of sepsis [12]. Thus, culture-negative sepsis contributes to high antibiotic consumption in neonatal units. Many neonates are therefore diagnosed with a "probable" or "possible" sepsis or a presumed symptomatic infection, but no bacterial cause is identified. These are often called culture-negative sepsis and will be treated for an average of 5 to 7 days [12, 14].

Some known effective ways of preventing neonatal sepsis include hand hygiene (HH), using soap and water or alcohol hand rub, appropriate well-defined care bundles or multimodal IPC programs, trophic enteral feeding and promoting early breastfeeding and skin-to-skin contact when the mother practices kangaroo mother care (KMC) [1,14-17].

The current evidence suggests HH compliance can be improved by posters, training, support from management and peers, champions, regular HH observation and availability of resources [16, 18-23].

ANTIBIOTICS STEWARDSHIP PROGRAMMES

An antibiotics stewardship program (ASP) is defined as a coordinated intervention designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regime, dose, duration of therapy, and route of administration and ensuring optimal patient outcome [15].

ASPs have been in existence and implemented at various degrees since 1996, with improvement over time. An ASP can be done by either restricting the use of reserved antibiotics or by prospective audit and feedback. Physicians and hospital pharmacists must collaborate and educate the rest of the HCW team in their ASP [5, 24].

Every systemic antibiotic administered to a patient has the potential to lead to antimicrobial resistance. It is estimated that over 50% of neonatal sepsis prescriptions are unnecessarily prescribed. Overusing antibiotics paves the way for the development of multi-resistant bacteria, and there is an urgent call for the rational use of antibiotics. In its global action plan, WHO recommended improved antibiotic surveillance as one of its key strategies to reduce the use of antibiotics [8, 25, 26].

Modalities of conducting Antibiotics Stewardship Programs

Antimicrobial stewardship programs in NICUs highlight the potential for improving antibiotic prescription practice by reducing broad-spectrum antibiotic therapy in vulnerable, very preterm infants [27, 28]. Antibiotic stewardship programs can be conducted in various ways depending on the facility's needs. Examples include the following methods described below.

Point of prevalence survey (PPS)

A PPS is a cross-sectional study done by reviewing patients' files admitted in the unit at the time of the study using a standardised tool appropriate for the facility level. The results of the PPS will rank the facility in adherence to ASP [27, 29].

The tool is used to review the use of antibiotics for in-patients. It helps to identify if the prescription was based on the guidelines, the blood culture results and if the antibiotics were given on time. It was

developed by the WHO and has been designed to be used at different levels of health care. The ASP team needs to take a course that is available online before conducting an ASP [25].

Mixed study combination

This method combines PPS and an intervention package to address an ASP in the facility. An ongoing assessment of the impact of the intervention will be done at 3, 6, and at 9-month intervals. It is coordinated as follows [25, 30-32]:

1. Point of prevalence survey:

   This is done at baseline and at identified intervals to assess ASP in the facility.

2. Intervention:
   The intervention package is prepared based on the preliminary findings of the baseline.

3. Education:

   The research team takes an online ASP course, conducts the PPS, and prepares an intervention package specific to the facility.

4. Leadership:

   The team leader can be a clinician in the area of interest, working closely with the hospital pharmacist, the infection prevention team (microbiologist/ nurse) and the quality assurance team. For a successful program, commitment from the hospital's executive management is required.

5. Prospective audit feedback:

   Ongoing PPSs are conducted to assess adherence to the ASP, and feedback is given to the healthcare workers (HCWs). This can also be used as a separate tool for the facility with an existing ASP program [32, 33].

Auto stop tool.

In this method, a facility with an already well-controlled ASP will design an auto-stop tool for empirical antibiotics. The hospital pharmacist is given access to patient laboratory results and can review and stop issuing the antimicrobial unless there is a documented reason to continue with treatment.

S. Sing et al. demonstrated that the auto-stop tool could reduce unnecessary antibiotic exposure in NICUs. In their study, the tool reduced exposure to ampicillin and gentamicin by 28% from baseline during the first week of life among VLBW infants [31].

Systemic reviews and meta-analyses demonstrated that most successful ASPs incorporate prospective audits and feedback, sepsis risk calculators, automatic stops for empiric antibiotics, structured guidelines, and the use of biomarkers [33, 40-42].

RATIONALE

An effective ICU ASP has been documented to result in [8, 24, 33]:

- Improving the quality of patient care in terms of improving rational antibiotic use.
- Reducing the prevalence and incidence of antimicrobial-resistant pathogens.
- Reducing cost expenditure in terms of antibiotics and consumables.
- Reducing the length of hospital stay.
- Decreasing the rate of central line infection.

The PPS and hand hygiene audits among healthcare workers are useful tools to identify gaps for strengthening antimicrobial stewardship activities. The infectious disease team of the hospital in another department can apply the same modality.

1.2 ETHICAL CONSIDERATIONS

This study was approved by the UCT Faculty of Health Sciences Health Research Ethics Committee (FHS HREC) with ethical approval number 613/2020. This study posed no risk to the patients. Information leaflets were provided to parents/ caretakers whose babies were admitted to the unit. The HCWs were informed about HH audit that was done and received a leaflet about ASP audit.

1.3. AUTHORS' GUIDELINES OF THE JOURNAL IN WHICH THE PAPER HAS BEEN FORMATTED

This study has a manuscript formatted for submission to Springer: Maternal and Child Health journal.

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CHAPTER 2: PUBLICATION-READY FORMAT

STRENGTHENING ANTIBIOTICS STEWARDSHIP AT MOWBRAY MATERNITY HOSPITAL– NEONATAL UNIT

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ABSTRACT

Objective To assess antimicrobial usage, prescription practices, sensitivity patterns, hand hygiene (HH) practices and adherence to antibiotic stewardship principles in the neonatal unit at Mowbray Maternity Hospital (MMH).

Study design: Mixed method observational study was done at MMH. A point of prevalence survey to assess antibiotic stewardship and HH audits were conducted using the WHO tools in two phases, a baseline in December 2020 and post-intervention from March to May 2021.

Results: 246 Neonatal unit patient folders were reviewed between December 2020 and May 2021. At baseline, compliance with treatment guidelines was 90% which improved to 100% post-intervention. We found 37(15.0%) babies were on antibiotics, with 64.9 % of those on first-line antibiotics (Access group). Using multivariate logistic regression, extremely preterm infants were more likely to be on antibiotics with an odds ratio of 11, which was statistically significant. We found eight organisms (18.9%), which included one Carbapenem-resistant enterococci -*Klebsiella pneumoniae.* For HH, a total of 444 opportunities were observed. Moment 5 had the lowest overall mean compliance of (57.4%), which was statistically significant with a p-value =0.0172. The overall HH compliance was 83.7% at baseline and 80.9% post-intervention; however, this was not statistically significant (p-value = 0.909).

Conclusion: Strict adherence to treatment guidelines and good HH are essential factors for the good antibiotic stewardship seen at the MMH neonatal unit. This was reflected by low antibiotic usage, good HH compliance and low HAI rate. Further improvement requires ongoing HH audits and training, especially focusing on HH moment 5, after touching the patient's surroundings.

Introduction

An antibiotic stewardship program (ASP) is defined as a coordinated intervention designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regime, dose, duration of therapy, and route of administration [1]

The first ASP studies were published in the late 1990s, and publications have increased exponentially over the last two decades. An ASP can be done by either restricting the use of reserved antibiotics or prospective audit and feedback. Physicians, hospital pharmacists, and the nursing team must collaborate and educate the rest of the healthcare team in their ASP [2, 3].

Every systemic antibiotic administered to a patient has the potential to lead to antimicrobial resistance [7]. It is estimated that over 50% of neonatal sepsis prescriptions are unnecessarily prescribed [4 – 7]. Overusing antibiotics paves the way for developing multi-drug resistant bacteria, and there is an urgent call for the rational use of antibiotics. In its global action plan, WHO recommended improved antibiotic surveillance as one of its key strategies [4-7]. Children being a special group, the Essential medicine list for Children (EMLc) is used (4) to classify antibiotics into three categories, namely the Access group, the Watch group and the restricted group (AWaRE) [4]. Antimicrobial stewardship programs in NICUs highlight the potential to improve antibiotic prescription practice by reducing broad-spectrum antibiotic therapy in vulnerable preterm infants [7, 8].

Although the incidence of culture-proven sepsis is declining worldwide [9], antibiotic use for culture-negative sepsis in the absence of a positive blood culture has remained to be around 6 to 16-fold more than for confirmed sepsis [10, 11]. A study done in South Africa showed the rate of positivity in blood cultures is approximately 8%, while empirical antibiotic use was 46.7% which suggests over-treatment of sepsis [11, 12]. Thus, culture-negative sepsis contributes to high antibiotic consumption in neonatal units [11-12] Many neonates are

therefore diagnosed with “probable” or “possible” sepsis or a presumed symptomatic infection, but no bacterial cause is identified. These are often called culture-negative sepsis and will be treated for an average of 5 to 7 days [11, 13].

Some effective ways of preventing neonatal sepsis include HH, using soap and water or alcohol hand rub, appropriate well-defined care bundles or multimodal IPC programs, trophic enteral feeding, and promoting early breastfeeding [1, 14-17].

There are various ways of improving compliance with HH among healthcare workers and parents. The evidence suggests HH compliance can be improved if there are posters of HH, training, support from management and peers, HH champions, regular HH observation, and availability of resources for hand hygiene [16, 18-23].

Materials and Method

The study was conducted at the MMH Neonatal Unit, a 73 bedded Neonatal Unit which offers all levels of neonatal care, including a NICU, high care, special care, pre-discharge, and kangaroo mother care unit. MMH is a busy, regional, level II obstetric referral hospital with an average of 900 births per month, 11000 per year. The neonatal unit admits patients delivered at MMH and referrals from six primary midwife obstetric units, 2 district hospitals, and private hospitals in the immediate surrounding catchment area. MMH is the referral centre for approximately 20,000 babies born per year in the Metro West geographical area of the Western Cape. The clinical team consists of three consultants (1 neonatologist, 2 general paediatricians), one neonatal fellow, nine medical officers, two rotating registrars, two junior intern doctors who rotate every two months, two community service doctors every six months, and approximately 15 nursing staff daily.

Study period

Phase 1: Baseline study (December 2020)

This was conducted in December 2020. It involved a PPS and HH audit for that month. The results were analysed and used for intervention.

Intervention: January and February 2021.

The findings from the PPS and HH audits' baseline in December 2020 were presented to the HCWs working in the neonatal unit and HH training (in small groups) were done by the IPC nurse to day- and nightshifts HCWs.

P**hase II: Post-intervention, March-May 2021**

The PPS was done for three months in March, April, and May 2021. The second HH was done in May 2021.

Point of prevalence survey (PPS)

All newborns admitted to the unit before 10 am on the day of data collection were eligible for the study. The data collection was done on the same day for the entire unit. Data were collected from the patient's files, and blood results were accessed from the National Health Laboratory service portal using the adapted WHO PPS tools.

Inclusion criteria

All files for babies admitted before 10:00 am were reviewed on the data collection day.

Exclusion criteria

All babies admitted after 10 am on the day of data collection were excluded.

Observation for hand hygiene (HH)

HH practice of HCWs working in the neonatal care unit were observed anonymously for both day and night shifts. The observer recorded separately for doctors and nurses. The HH observation was done using a WHO HH tool, and the opportunity for the five moments HH were observed. Data was collected in December 2020 (baseline) and May 2021 (post-intervention). The five moments of HH as defined by WHO in figure 1.

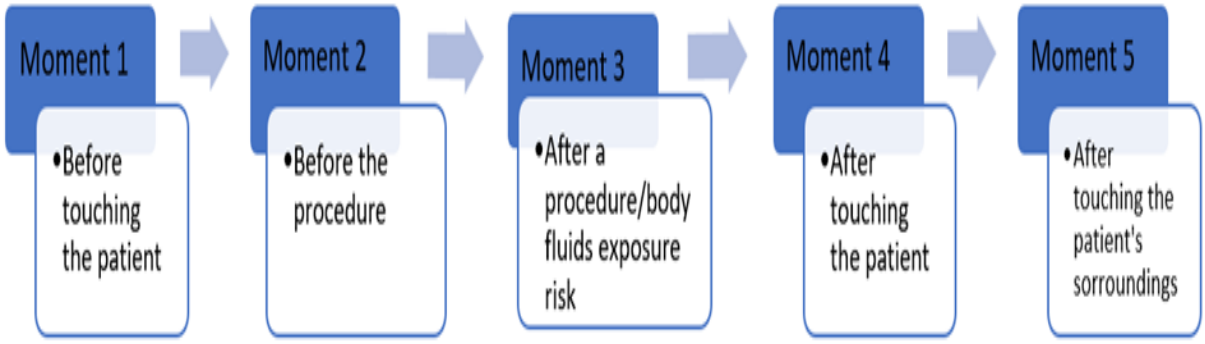


Figure 1: Moments of hand Hygiene

Intervention: Audit feedback and training of healthcare workers

The baseline HH and PPS audits were analysed, and audit feedback was provided during the formal doctors and nurses meeting. We reminded all doctors of the importance of adherence to the neonatal treatment protocol, and the latest changes were emphasised. All HCWs were given the opportunity to ask questions for clarification. In addition to the audit feedback, the team had sessions of HH protocol training by the IPC nurse in small groups during their working shifts.

Note: Staff changes were noted for both doctors and nurses. The unit recruited a junior doctor who was not around at the time of baseline assessment and audit feedback, and the routine changing of intern doctors every month continued. The neonatal unit nursing team had three seniors leaving and two new nurses joining the team in the midst of our study period.

Ethics

We explained to the parents why we reviewed their babies' files and provided them with an information leaflet. The HCWs in the unit were also informed about HH audits and were given a leaflet to read on ASP. There was a waiver of consent for reviewing patient files and observing HH as they are quality improvement activities.

This study was approved by the Faculty of Health Sciences Health Research Ethics Committee (FHS HREC) with ethical approval number 613/2020.

Analysis:

Multiple linear logistic regression was used to assess the relationship between the outcome variable (antibiotic use) with independent variables(sex of the baby, gestational age, area of admission, birthweight, inpatient days, baby age and birth location). Analysis of variance (ANOVA) was used to find the statistical difference in mean scores across the five HH moments. Two sample t-test was used to find if there is a statistical difference in HH compliance between cadres and overall mean compliance in 2020 (baseline) and 2021 (post-intervention). The analyses were done using Stata version 17.0. A p-value = 0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 246 baby folders were reviewed for baseline and post-intervention. Of the study participants, 53% of the study patients were female, and a third of the babies, 93 (37.8%), were admitted to the unit for 8 – 28 days. The median length of stay was in the ward was 13 days. Most of the babies, 209(85%), were not prescribed antibiotics when the PPS was conducted (table 1).

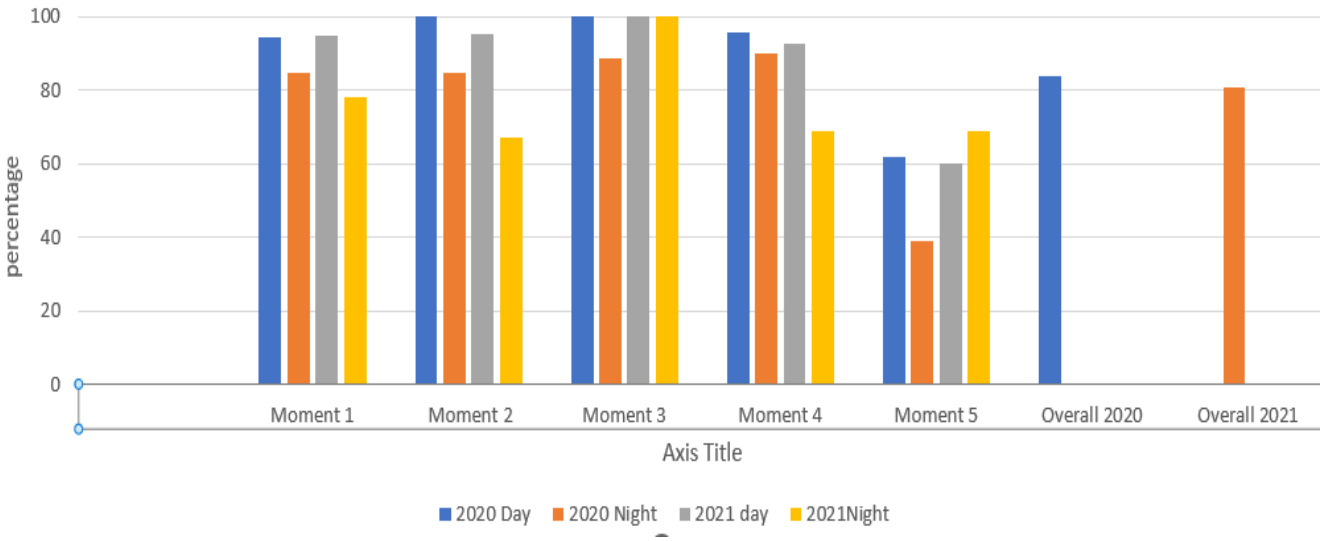
PPS findings

There were 37(15%) babies on antibiotics during the entire study period. We had eight organisms (18.9%), as shown in Table 1. The organisms isolated from the blood culture results were *E. coli* (2), *Group B streptococcus* (2), *Klebsiella pneumoniae* (CRE) 1, *Stenotrophomonas maltophilia* (1), *Coagulase negative Staphylococcus* (1), and one baby had congenital syphilis. Using the AWaRe classification, of the patients that were on antibiotics, 27(64.9%) were in the Access group, while 12(35.1%) were in the Watch group (Meropenem). There was no baby on restrictive antibiotics (table 2). Babies with a birth weight <1500gm were more likely to be on antibiotics, and this was highly statistically significant with a p-value < 0.0001. At baseline, there were 11 babies on antibiotics, and 10 (90.9%) of them had antibiotics prescribed according to the treatment guideline. This improved to 100% post-intervention (table 4). Babies admitted into the NICU were more likely to receive antibiotics than those admitted to the other areas; this was highly statistically significant with a p-value < 0.0001 (table 5).

Compliance to HH

A total of 444 HH opportunities were observed for both day and night shifts (inclusive of baseline and post-intervention). For the baseline, 224(50.4%) HH opportunities were observed, while there were 220(49.6%) HH opportunities post-intervention.

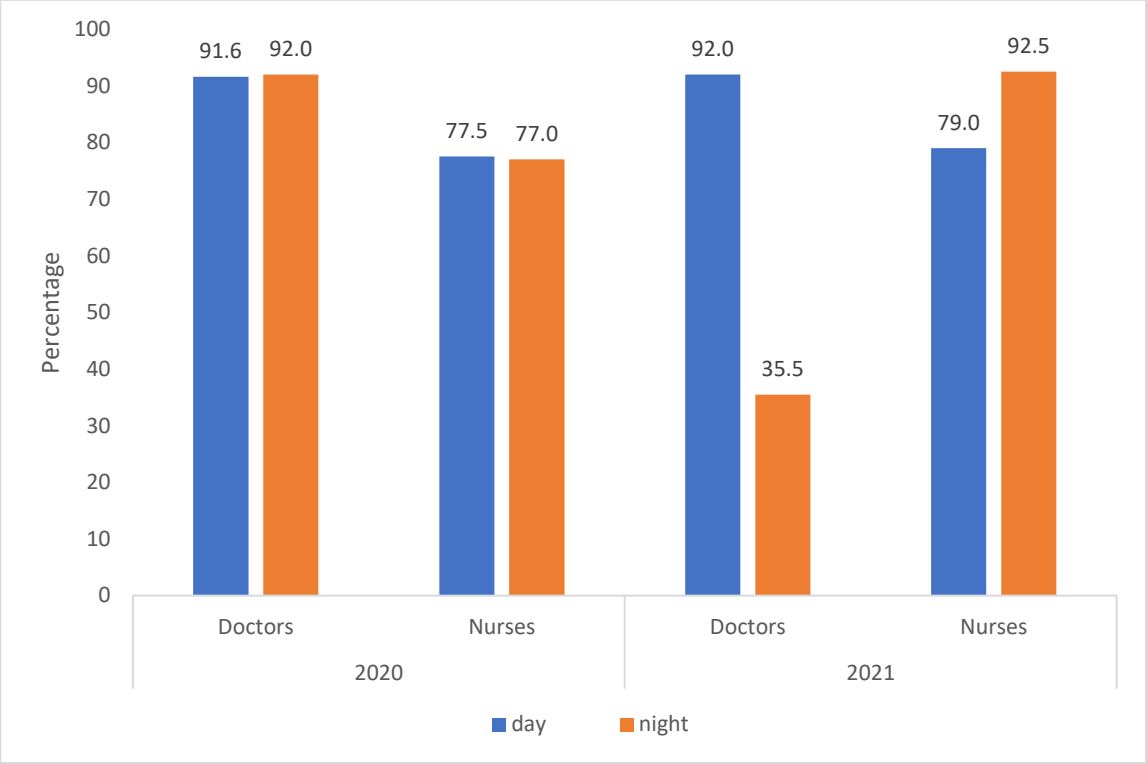
Figure 2



Compliance to HH across the five moments and Overall HH compliance for baseline (2020) and post-intervention (2021).

At baseline, the mean compliance for moment 3 was 94.4% and improved to 100% after the intervention. Comparing the mean compliance for the five moments of HH, using ANOVA, moment 5 had the lowest overall compliance, 57.4%, and was statistically significant with a p-value =0.0172. The overall mean HH compliance for mean HH was 83.7% at baseline and 80.9% post-intervention; however, this was not statistically significant (p-value = 0.909).

Figure 3



Compliance with HH for both doctors and nurses at baseline (2020) and post-intervention (2021).

The tables show that doctors showed good compliance in day and night at baseline (2020) compared to nurses, while nurses scored higher in compliance during the night shift post-intervention (2021). The difference was statistically significant using a t-test p-value =0.0033.

DISCUSSION

This quality improvement study was done at the Mowbray Maternity Hospital neonatal unit. A baseline PPS and HH observation audit were conducted, followed by an intervention (audit feedback to staff, 'gentle reminders' and HH training) and post-intervention subsequent PPSs and another HH audit. This study found a very low antibiotic usage at MMH and rational use of antibiotics attributed to high compliance to protocols with the "Access" antibiotics used in 64.9% of cases. The overall HH behaviour was good pre- and post-intervention, best for moments 1-4, least in moment 5- observed after touching the patient's surroundings.

Antibiotics are commonly used in the neonatal unit, and Ampicillin [24] and Gentamycin were used in 72.9 % of cases in our study, similar to Newby et al study [25]. From our study, the causative organisms in early-onset sepsis were mainly caused by GBS and congenital syphilis, while gram-negative organisms caused HAI. These causative organisms are similar to studies conducted in LMICs [12, 26, 27] and other high-income countries [27, 28], except for congenital syphilis, which was not previously reported. This is possibly a result of the Covid pandemic, with restricted general health and STI treatment access [29, 30]. Using the Essential medicine list classification for children (EMLc), our study did not have any babies in the restricted antibiotics group, contrary to the study done by Hsia Y et al [4]. This difference may be attributed to strict adherence (100% post-intervention) to the MMH unit's neonatal treatment guideline and a low rate of HAI when compared to many LMIC neonatal units [34-37].

PPS is one way of assessing the rational use of antibiotics in a NICU [31, 32]. The results from our PPS showed neonatal sepsis was found only in 8 babies (3.2%), a lower rate compared to many LMIC neonatal units [34-37]. Our neonatal unit has a low antibiotic utilisation rate of 15%, lower than the 48% shown by Hufnagel et al [33]. This may be partly because we only had one surgical patient in our study participants since surgical patients are often on prophylactic antibiotics.

The practice at MMH includes prescribing according to the treatment protocol and stopping antibiotics if the inflammatory markers (mainly CRP) are not suggestive of infection and a negative blood culture after 48 hours of incubation. Our study has shown that MMH has high compliance to the standard protocols, which improved to 100% post-intervention. Adherence to treatment protocol is an important aspect of ASP since it lowers the rate of antibiotic use in especially in premature babies [36, 38] and eventually reduces in-hospital days and a lower rate of HAI and NEC [33, 38].

HH compliance has been shown to improve with pre-assessment and training models [23, 40]. Our study showed good overall HH compliance, mean of 82,3%. This finding is above the average of 60 -70% in most facilities as shown in a systematic review by [41,42].

Nurses have been shown to have better compliance than doctors [43]. Our study had similar findings where nurses had higher mean compliance than doctors. We also observed a decline in compliance post-intervention which was mostly contributed to by doctor HH compliance. This may have been partly due to new medical staff, but possibly more importantly, the HH training was more organised for the nursing team [43].

Similar to other studies, we have demonstrated variation in compliance to opportunities of HH [39 – 47]. HH moment 3, required after any procedure or contact with body fluids, was found to have the highest mean compliance rate at 97.2%. This may be because of a perception of the high risk of contamination after touching body fluids [39] and the availability of alcohol hand rub [16,20, 39 – 45]. The high rate may also be because this study was done during the Covid pandemic, where HH was emphasised as means to reduce the risk of viral contamination [39, 43].

We found that HH moment 5, after touching the patient's surroundings, showed the least overall compliance. Although we did not assess the reasons for poor compliance, studies have

shown poor compliance is affected by behavioural factors, awareness of HCWs to HH opportunity, availability of alcohol hand rub, and overall altitude, thus emphasising a need for continued training, use of posters and supply of appropriate alcohol at bed-side for HH [45-47].

Conclusion and recommendation

Our study is among a few PPS and HH audits done at neonatal units in LMICs [4,6,7,9,26, 32]. The availability of clear and strict guidelines for antibiotic use and the use of laboratory results are important for minimising the unnecessary use of antibiotics in neonatal units. Good HH practice further minimises the risk of HAIs and reduces exposure to antibiotics and the development of antibiotic-resistant infections. Training HCWs and audit feedback are important aspects of QI in a neonatal unit. These are all cost-effective measures that neonatal units in LMICs can adopt to reduce preventable neonatal deaths due to infection.

For MMH neonatal unit, repeating a similar study, especially post the COVID pandemic, "HH and disinfectant-sensitized" era will be useful. Future studies could include antibiotic hang times (time of administration after prescription) and stop times (≤48hrs) and attempt to estimate clinical outcomes over time in relation to the calculated antimicrobial consumption by defined daily dose (DDD).

Limitation

Some of our results had small numbers and may not be generalised. We did not calculate the antimicrobial consumption by defined daily dose (DDD) and estimations of clinical outcomes related to antibiotic treatment because of our study design.

While the moments of HH are well described in the literature, it would be useful to know what HCWs knowledge and perceptions are on each moment to better understand the barriers and enablers to HH. These are all potential focus areas for future studies.

Acknowledgement

I would like to thank the African Paediatric Fellowship Program and DAAD for sponsoring my sub-speciality training in neonatology which has led to this research. To the MMH neonatal unit and the infection prevention and control nurses, Sr Engelbrecht and Sr Aucamp, who supported my research. My supervisors, Dr Van Niekerk and Dr Rhoda who supported me throughout this research. To my husband George, I owe eternal gratitude for his unwavering support and understanding throughout my two-year fellowship training, especially during the COVID pandemic, when we could not see each other as often as planned.

Authors contributions

1. MM was responsible for designing the study proposal, writing the protocol and report, interpreting results, and looking up references.
2. JS was responsible for editing the protocol and data analysis and interpreting the results.
3. AVN was responsible for designing the study proposal, analysing the data, and editing the report.
4. HE was responsible for data collection, analysis and referencing.
5. NRR was responsible for designing the study protocol, analysis, editing the report and referencing.

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Conflict of interest

None declared.

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APPENDICES

Table 1: Baseline characteristics of admitted newborns (n=246)

Variable	**n (%)**
Newborn sex	
Female	131(53.2)
Birthweight (g)	
>500 - 1499 g	119(48.3)
1500–2499 g	84(34.2)
2500–4500g	43(17.5)
Gestational age (weeks)	
Very preterm (<34)	98(39.8)
Very preterm (<34)	98(39.8)
Late preterm (35 - 37)	96(39.1)
Term (>37 -42 weeks)	*52(21.1)*
Age group (postnatal days)	
0-3	38(15.5)
4-7	48(19.5)
8-28	95(38.6)
>28	65(26.4)
Median age	13 days (interquartile range 5 – 30)
Admission area	
NICU	45(18.3)
High and standard care	157(63.8)
KMC	44(17.9)

Total hospital days	
0-3	40(16.3)
4-7	48(19.5)
8-28	93(37.8)
>28	65(26.4)
Use of Antibiotics	
Yes	37(15.0)
No	209(85.0)
Blood culture positivity rate	
Blood culture positive	8(21.6)
Blood culture negative	29(78.4)
Use of antibiotics according to phases	
Baseline	10(27)
Post-intervention	27(73)
Use of antibiotics based on BWT	N = 37
<1000gm	8(21.6)
1000 – 1499gm	6(16.2)
1500 – 2400gm	14(37.8)
2400 – 3999gm	9(24.3)
>4000	5(13.5)

Notably, female babies comprised 53% of the study patients; a third of babies, 93 (37.8%) were admitted for 8 – 28 days, and most of the babies, 209(85%), were not on any antibiotics. Of those on antibiotics, babies < 1500gm were 14(37,8%) had only one antibiotic encounter. The isolated organism were *E. coli* (2), *Group B streptococcus* (2), *Klebsiella pneumoniae* (CRE) 1, *Stenotrophomonas maltophilia* (1), *Coagulase negative Staphylococcus* (1), and one baby had congenital syphilis.

Table 2: Patient encounter with antibiotics based on the AWaRE Classification. (N = 37)

Classification group of antibiotics	**Name of antibiotics**	**Number of times encountered with antibiotics**				
		1	**2**	**3**	**4**	**Total (%)**
Access (first line)	Ampicillin & gentamycin	22	0	0	0	22(59.5)
	Penicillin	1	0	0	0	1 (2.7)
	Cloxacillin	1	0	0	0	1(2.7)
						24(64.9)
Watch (second line)	Meropenem	3	6	3	1	13(35.1)
	Total	**27(73)**	**6(16.2)**	**3(8.1)**	**1(2,7)**	**37(100)**

From the table, 24(64.9%) of the antibiotics fall under the Access group. Overall, 27(73%) cases had only one antibiotic encounter.

Table 3: Birth weight in relation to total days of hospitalisation.

	TOTAL HOSPITAL DAYS					
Birth weight (g)	**0 -3**	**4 - 7**	**8 - 28**	**>28**	TOTAL	
500 - 1499	4(10.0)	14(29.2)	50(53.8)	51(78.5)	119(48.4)	
1500 - 2499	18(45)	27(56.3)	30(32.3)	9(13.9)	84(34.1)	
2500 - 4500	18(45)	7(14.6)	13(15.0)	5(7.7)	43(17.5)	X^2 =
Total	40(16.2)	48(100)	93(37.7)	65	246	<0.0001

93 babies (37.7%) had a hospital duration of 8 – 28 days. Babies with small weights <1500g) had longer hospital admission days than bigger babies with birth weight >1500gm, with a high statistical significance. (p-value = 0.0001)

Table 4: Prescription of antibiotics based on the treatment guideline.

		Prescription according to guideline		(%)
	Not on antibiotics	Yes	No	Total
Baseline	58	10 (90.9)	1 (9.1)	69
Post-intervention	151	26(100)	0 (0)	177
Total	209	36(97.3)	1(2.7)	246

At baseline 10(90.9%) had the antibiotics prescribed according to the treatment guideline.

Table 5: **Multivariate logistic regression of factors associated with the utilisation of antibiotics for babies admitted in the neonatal unit.**

Covariates	**Odds ratio**	**Confidence interval (CI)**	**P-value**
Newborn sex			
Female (reference group)			
Male	0.99	(0.49-2.51)	0.94
Gestational age			
Extreme preterm (reference group)			
Very preterm	1.16	(0.19-7.10)	0.67
Moderate preterm	11.28	(0.64 -197.17)	0.07
Late preterm	11.12	(0.78 – 157.70)	0.08
Term	12.36	(0.69 – 220.05)	0.09
Area of admission			
NICU (refence group)			
High care	3.61	(1.32 - 9.84)	0.01
KMC	3.58	0.74 - 17.46)	0.10
Birth weight			
<1000 (reference group)			
1000 - 1499	4.04	(0.55 - 29.58)	0.17
1500 - 2499	1.22	(0.10 - 14.47)	0.90
2500 - 4000	0.73	(0.04 - 12.60)	0.80
Inpatient days			
0-3 (reference range)			
4 - 7	0.001	0	0.99
8 - 28	0.0001	0	0.99
>28	64.84	(8.6 – 485.72)	<0.0001
Place of birth			
In hospital (inborn)			
Outborn	0.74	(0.17 – 4.54)	0.74
BBA	1.71	(0.00 – 35.10)	0.71

The result from logistic regression shows that babies who stayed more than 28 days in the ward were more likely to use antibiotics than those who stayed shorter (OR=64., 95% CI 8.6-485.7). Moreover, babies admitted to the high-care unit had a higher likelihood of using antibiotics than those in the NICU.

ETHICAL APPROVAL

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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12 November 2020

HREC REF: 613/2020

Dr N Rhoda
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Dear Dr Rhoda

PROJECT TITLE: STRENGTHENING ANTIBIOTICS STEWARDSHIP AT MOWBRAY MATERNITY – NEONATAL UNIT-MPHIL CANDIDATE-DR MARTHA MKONY

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 November 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Martha Mkony will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

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Contents

- Instructions for Authors
  - Editorial Procedure
  - Manuscript Submission
  - Integrity of Research and Reporting
  - Formatting Requirements
  - Electronic Supplementary Material
  - Tables
  - Artwork and Illustrations Guidelines
  - Research Data Policy
  - Editing Services
  - Springer Open Choice
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- Open access publishing
- Mistakes to avoid during manuscript preparation

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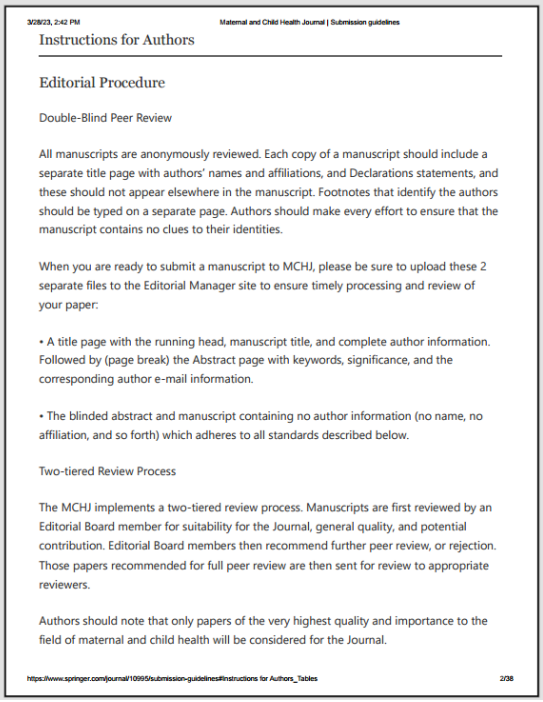

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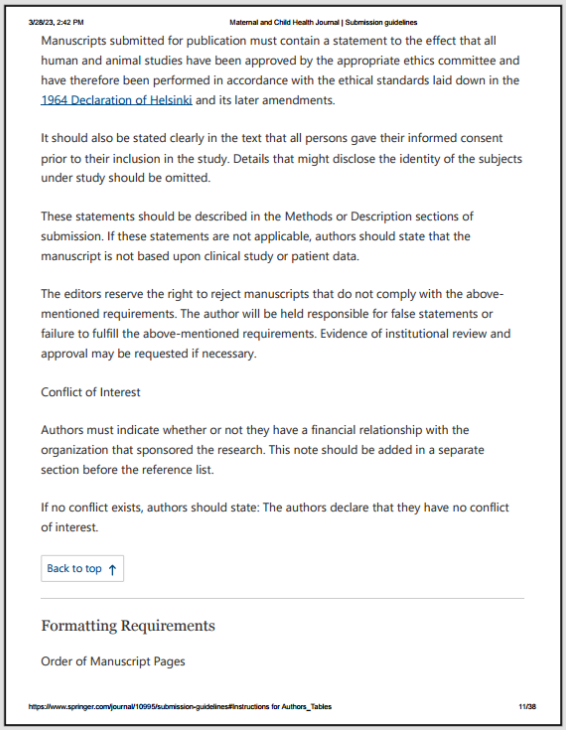

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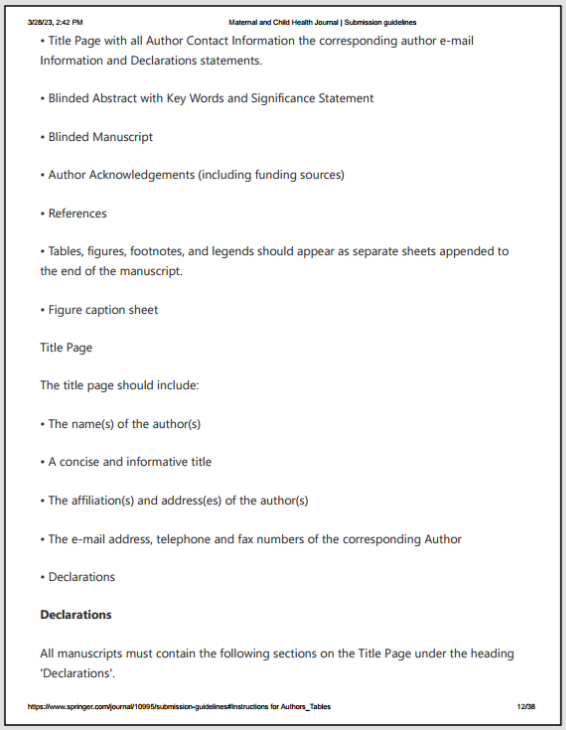

3/28/23, 2:42 PM Maternal and Child Health Journal | Submission guidelines

• Title Page with all Author Contact Information the corresponding author e-mail Information and Declarations statements.

• Blinded Abstract with Key Words and Significance Statement

• Blinded Manuscript

• Author Acknowledgements (including funding sources)

• References

• Tables, figures, footnotes, and legends should appear as separate sheets appended to the end of the manuscript.

• Figure caption sheet

Title Page

The title page should include:

• The name(s) of the author(s)

• A concise and informative title

• The affiliation(s) and address(es) of the author(s)

• The e-mail address, telephone and fax numbers of the corresponding Author

• Declarations

Declarations

All manuscripts must contain the following sections on the Title Page under the heading 'Declarations'.

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If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

• Funding (information that explains whether and by whom the research was supported)

• Conflicts of interest/Competing interests (include appropriate disclosures)

• Ethics approval (include appropriate approvals or waivers)

• Consent to participate (include appropriate consent statements)

• Consent for publication (consent statement regarding publishing an individual's data or image)

• Availability of data and material (data transparency)

• Code availability (software application or custom code)

• Authors' contributions

Please see the relevant sections in the submission guidelines for further information.

Abstract

A structured abstract of up to 250 words is to be provided. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article.

• For Original Research articles using the headings: Objectives, Methods, Results, and Conclusions for Practice.

• For From the Field articles use the headings: Purpose, Description, Assessment, and Conclusion.

• Another acceptable format for all article types is: Introduction, Methods, Results, and Discussion.

Significance

Directly after the Abstract, the author should include a short paragraph (100 words or less) titled "Significance" which addresses what is already known about the topic of their article and what their article adds to the literature.

For example, the following paragraphs were included in "The educational gradient in coronary heart disease: the association with cognition in a cohort of 57,279 male conscripts" by Inger Ariansen, Laust Mortensen, Jannicke Igland, Grethe S Tell, Kristian Tambs, Sidsel Graff-Iversen, Bjørn Heine Strand, and Øyvind Næss in J Epidemiol Community Health available here: http://jech.bmj.com/content/early/2014/11/13/jech-2014-204597.full.pdf+html

"What is already known on this subject?

The socioeconomic gradient in coronary heart disease may not be fully explained by social differences in cardiovascular risk factors. Cognitive ability has been proposed to impact this gradient independently of cardiovascular risk factors.

"What this study adds?

Adjustment for established cardiovascular disease risk factors substantially attenuated the educational gradient in coronary heart disease. Although the remaining unexplained gradient was not further attenuated by cognitive ability, cognitive ability alone

Statistical Reporting

Manuscripts should confirm to the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines, which can be found at http://www.equator-network.org/reporting-guidelines/sampl/.

Manuscript Formatting Considerations

Text Formatting

Manuscripts should be submitted in Word.

• Use a normal, plain font (e.g., 12-point Times Roman) for text.

• Use italics for emphasis.

• Use the automatic page numbering function to number the pages.

• Do not use field functions.

• Use tab stops or other commands for indents, not the space bar.

• Use the table function, not spreadsheets, to make tables.

• Use the equation editor or MathType for equations.

• Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

• Please use no more than three levels of displayed headings.

o Level 1: Centered

o Level 2: Centered Italicized

o Level 3: Flush left, Italicized

• For Original Research articles using the headings: Objectives, Methods, Results, and Conclusions for Practice.

• For From the Field articles use the headings: Purpose, Description, Assessment, and Conclusion.

• Another acceptable format for all article types is: Introduction, Methods, Results, and Discussion.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Scientific Style and Terminology

• The Journal prefers that authors refer to "woman/women" instead of "mother/mothers" unless the paper is directly referencing the woman's own role as a parent.

Color Art

- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted within the body of the text. Only if the file size of the manuscript causes problems in uploading it, the large figures should be submitted separately from the text.
- When preparing your figures, size figures to fit in the column width.
- For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
- For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

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- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)