A Case-control review of neonates with Meconium Aspiration Syndrome admitted to a Tertiary Hospital in Johannesburg, South Africa

Lara Alexandra Jones

0200983G

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of the Master of Medicine in the branch of Paediatrics

24 January 2019

DECLARATION

I, Lara Jones, declare that this research project is my own original work. I am aware that plagiarism is wrong. This research report is being submitted for the degree of Master of Medicine in Paediatrics at the University if the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other institution.

LAJones

L. Jones
24 January 2019

AKNOWLEDGEMENTS

I would like to say a special thanks to my supervisor, Professor Ballot for her unwavering encouragement and expert guidance and patience throughout the process of writing this report. I would never have finished it without her.

This report would not have been possible without the neonatal database, a priceless tool to the department and therefore I would like express my gratitude to Milton Reineke and Lebogang Rapola who aid in data collection and capturing.

Last but not least, I would like to express my thanks to my family for their endless encouragement and support.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

MAS:	Meconium aspiration syndrome
PPHN:	Persistent pulmonary hypertension of the newborn
iNO:	Inhaled nitric oxide
HFOV:	High frequency oscillation ventilation
HIE:	Hypoxic ischaemic encephalopathy
SGA:	Small for gestational age
AGA:	Appropriate for gestational age
LGA:	Large for gestational age
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
NCPAP:	Nasal continuous positive airway pressure
LMICS:	Low-middle income countries
HIC:	High income countries
HIV:	Human immunodeficiency virus
ECMO:	Extra corporal membrane oxygenation

LIST OF FIGURES AND TABLES

SUBMISSABLE PAPER

A Case-control review of neonates with Meconium Aspiration Syndrome admitted to a Tertiary Hospital in Johannesburg, South Africa

L. Jones, MB BCh**; D. E. Ballot,** MB BCh**,** FCPaed (SA), PhD

Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

Corresponding author: *L Jones (joneslа3@gmail.com)*

ABSTRACT

Background: Neonates with meconium aspiration syndrome (MAS) represent a high-risk population. This study demonstrates the morbidity and mortality profile associated with this condition.

Objectives: To isolate characteristics, complications and outcomes of neonates with MAS admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and compare them with neonates born without MAS.

Methods: The study was a case-control retrospective review of neonates admitted to the CMJAH neonatal unit between 1 January 2013 and 30 April 2015.

Results: A total of 608 neonates were analysed. All cases were compared to the control group. The overall incidence of MAS was 7.6%. Neonates born with MAS had a higher mortality than controls (12.2% vs. 2.6%; p=0.001). Sixty-eight percent of neonates ventilated with MAS died. Neonates born with MAS were more likely to have a higher mean birth weight (3.1 kg vs. 2.6 kg) and to be term/post term (39.2 weeks vs. 36.2 weeks). Significantly more neonates with MAS were born small for gestational age compared to the control group (24.6% vs. 19.0%). Neonates with MAS were more likely to have poor Apgars (25.7% vs. 14.9%; p=0.001) and require ventilation (35.9% vs. 5.6%; p<0.001). Complications were higher in neonates born with MAS when compared to controls and included pneumothoraces (2.3% vs. 0.3%; p=0.003, PPHN (14.5% vs. 1%; p=0.001) and overall sepsis (13.3% vs. 7.6%; p=0.02). Factors associated with an increased mortality in the neonates with MAS were the development of HIE (p=0.001), PPHN (p=0.001) and the use of inotropes (p=0.001).

Conclusion: Meconium aspiration syndrome is an important cause of morbidity and mortality in a resource limited setting.

(261)

1.0 INTRODUCTION

Meconium aspiration syndrome (MAS) is an important cause of mortality and respiratory morbidity in the term and post term neonate.[1, 2] Approximately 3 to 4% of neonates born with meconium stained liquor will develop MAS.[3]

Meconium is sterile and composed primarily of bile, debris from desquamated cells and amniotic fluid. It can be found as early as 12 weeks gestation in the fetal gastrointestinal tract but its passage into the amniotic fluid is uncommon before 34 weeks gestation.[4]

Some important risk factors associated with the presence of meconium-stained liquor include fetal compromise, indicated by pathological fetal heart rates, abnormal cardiotocographs and, or low Apgar scores. Post maturity, chorioamnionitis and prolonged labour with subsequent necessity for Caesarean sections are also associated with a higher risk of MAS.[2, 5, 6]

The prevalence of meconium-stained liquor is strongly associated with gestational age and increases linearly from 37 weeks to 42 weeks gestation.[4]

Meconium aspiration syndrome causes diffuse inflammation of the lung parenchyma with release of cytokines and activation of macrophages, resulting in an associated meconium-induced pneumonitis.[4] Meconium has a thick, particulate consistency causing complete or partial airway obstruction when aspirated. Meconium also interferes with surfactant production. The combination of these two processes can cause severe respiratory failure with or without pulmonary hypertension, as well as air leak syndromes.[7] Neonates that demonstrate hypoxaemic respiratory failure often develop a respiratory acidosis and, or persistent pulmonary hypertension (PPHN).

Meconium aspiration syndrome is diagnosed in a neonate with respiratory distress born through meconium-stained liquor whose clinical picture cannot be attributed to any other cause. The clinical signs of MAS can vary from mild tachypnoea to severe respiratory distress, hypoxaemia and pulmonary hypertension.

The incidence of MAS in high-income countries (HIC) has decreased steadily over the last 15 years from 5% to 2%.[5, 6] Mortality rates ranged from 28% to 40% in studies from the 1970s and 1980s to less than 15% in recent literature.[8] The decrease in mortality is attributed to the improvement in obstetric practices (earlier intervention when fetal distress is noted and avoidance of post term deliveries).[8] The use of respiratory adjuncts, namely surfactant, inhaled nitric oxide (iNO) and high frequency oscillatory ventilation (HFOV) has decreased mortality rates in neonates with MAS, but has made little impact on duration of mechanical ventilation and oxygen therapy.[2]

At least one third of neonates presenting with MAS require intubation and mechanical ventilation.[2] Mechanical ventilation in neonates with MAS is still associated with a high morbidity and mortality in low-middle income countries (LMIC). This is attributed to delays in instituting treatment, limited access to adjunct respiratory therapies and intensive care beds. Patients frequently succumb to concomitant infections.[9, 10]

There is still much controversy regarding the effectiveness of postpartum intubation and suctioning in the prevention of MAS. Suctioning the nasopharynx with delivery of the head and endotracheal suctioning has not been associated with a decrease in respiratory distress in vigorous meconium exposed neonates when compared with expectant management.[11] Although tracheal suctioning has been suggested to improve the clinical course of MAS in non-vigorous meconium exposed neonates, no therapies to date have been definitively proven to be effective.[3] Meconium aspiration syndrome is most likely an antepartum event and cannot be prevented by post-partum suctioning of the neonatal airway.

The objectives of this study were to assess whether neonates with MAS presenting to CMJAH have increased morbidity and mortality profiles when comparing them to neonates without MAS. The identifying of characteristics associated with MAS may aid in establishing potential correctable factors causing poor clinical outcomes.

2.0 METHODS

Study Population

This was an unmatched, case control, retrospective review. The study population included neonates admitted to CMJAH neonatal unit between 1 January 2013 and 30 April 2015. Charlotte Maxeke Johannesburg Academic Hospital is a tertiary care institution which functions as a referral centre for primary health care clinics and secondary hospitals.

All neonates above 1500 g birth weight admitted to the neonatal unit within 72 hours of life were included in the study. Neonates with MAS were classified as the study group. All other neonates were considered for inclusion in the control group. Neonates with major congenital abnormalities and surgical conditions were excluded.

There were thirteen times more neonates in the sample group than in the study (neonates with MAS) group. Selecting every thirteenth baby from the sample group isolated 304 neonates without MAS for the control group. (See figure 1)

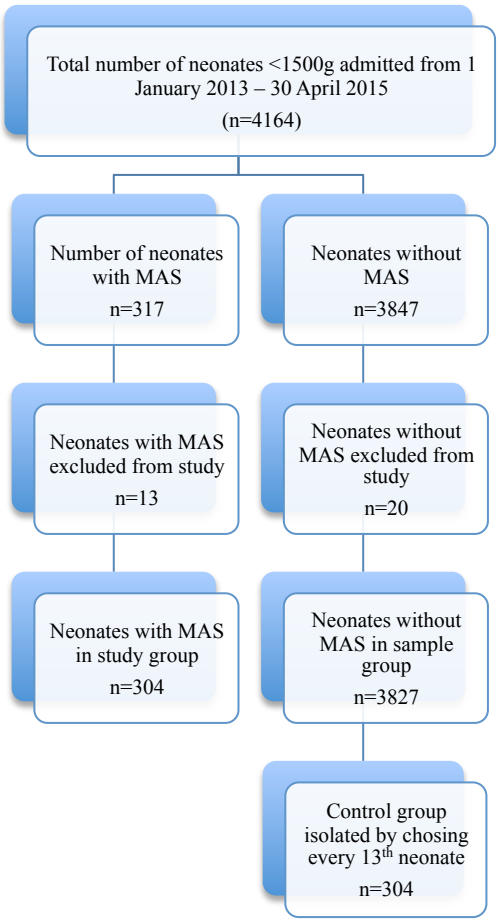


Figure 1: Selection of final sample

Definitions

Meconium aspiration syndrome was defined as respiratory distress in a meconium exposed neonate that developed within 1 hour of birth, with a PaO2 <50 mmHg in room air, central cyanosis in room air or supplemental oxygen to maintain a PaO2 >50 mmHg.[12] These clinical findings should be accompanied by an abnormal chest radiograph showing non-homogenous infiltrates, with areas of diminished aeration with or without hyperinflation.[13] Respiratory failure was defined as a pH <7.25, pC02 >55 mmHg on arterial blood gas and/or oxygen saturation <89% or pa02 <50 mmHg in 70% oxygen.[14] Neonates with MAS and early onset sepsis were classified as MAS and not congenital pneumonia. Sepsis included both early and late onset sepsis; some neonates had both. For our study purposes, neonatal resuscitation was defined as the need for assisted ventilation at birth.

Neonates were managed at the discretion of the attending neonatologist. Neonates with hyaline membrane disease who required nasal continuous positive airway

pressure (NCPAP) were given surfactant regardless of fraction of inspired oxygen. Not all neonates admitted with MAS were ventilated. Neonates with MAS who developed respiratory failure were placed on NCPAP if there was no ICU bed available. Bolus surfactant therapy was given to MAS neonates with moderate to severe respiratory distress requiring NCPAP or ventilation at the discretion of the attending physician.[10] This is based on evidence from the Canadian Paediatric Society, which recommends the administration of surfactant to all ventilated neonates with MAS if they require Fi02 ≥50%. Neonates diagnosed with MAS that required ventilation were started on conventional ventilation. Neonates requiring inotropes were started on either dopamine or dobutamine. If these neonates developed persistent pulmonary hypertension of the newborn (PPHN), they were started on Sildenafil if all other modalities failed. High frequency oscillatory ventilation was offered if increasing pressures were required to maintain adequate oxygenation. Inhaled Nitrous Oxide (iNO) or extra corporal membrane oxygenation (ECMO) was not available in our unit at the time of the study.

2.1 DATA COLLECTION

Demographic, obstetric and clinical data was routinely captured on discharge for each patient. The data was checked for completeness and validity. The data was managed using REDCAP (Research Electronic Data Capture).[15] This study was an analysis of the neonatal database.

Variables and definitions

Maternal information included maternal race, antenatal booking status, gestational age, parity, gravity, place of delivery, presence of chorioamnionitis, delivery mode and HIV status. Neonatal variables included final outcome, primary respiratory diagnosis, gender, growth adequacy, five minute Apgar score, need for initial resuscitation, inotropic support and the need for surfactant, NCPAP or ventilation. Furthermore, birth weights were plotted as small for gestational age (SGA), appropriate for gestational age (AGA) or large for gestational age (LGA) according to the Fenton growth chart.[16] Poor Apgar scores were defined as Apgars ≤6 at five minutes. Neonatal outcomes included development of pneumothoraces, HIE, PPHN or sepsis. The definition of early sepsis was a positive blood culture within 72 hours

of birth. The diagnosis of HIE was made using modified Sarnat staging and included mild, moderate and severe stages.[16] Persistent pulmonary hypertension was diagnosed as a preductal vs. postductal pulse oxymeter oxygen saturation gradient of more than 10%.[13]

2.2 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 23. Variables were compared between both case and control groups and survivors and non-survivors in the MAS group to isolate predictors of mortality. Continuous variables were described as means and standard deviations (SDs) as data had a normal distribution and categorical variables were described using frequencies and percentages. Univariate analysis was performed using Chi-Square tests of homogeneity to determine if there was a statistically significant difference in frequencies between cases and controls. Differences in means across cases and controls for normally distributed continuous variables were compared using two-sample t-tests. Binary logistic regression was done to isolate variables associated with MAS as well the risk factors associated with mortality in the MAS group. A p-value ≤ 0.05 was considered to be significant. Variables with a p-value <0.1 were entered into the logistic regression model. Cases with missing data were excluded from statistical analysis.

2.3 ETHICS

The Human Research Ethics Committee at the University of the Witwatersrand, Johannesburg approved the study. (Clearance certificate No. M160571)

3.0 RESULTS

A total of 4131 neonates with a birth weight greater than 1500 g, were left in the final dataset once cases had been excluded. There were 317 neonates admitted with a diagnosis of MAS. Among the 317 neonates, 13 were excluded, 7 with surgical conditions and 6 with congenital abnormalities. This left a total of 304 neonates with MAS in the final case sample.

Characteristics of final dataset

In this study, there were a total of 608 neonates analysed in the final dataset, 304 controls and 304 cases. Neonates with MAS accounted for 317/4164 (7.6%) of all neonates admitted to the unit during the study period. Male to female ratio was 1.4:1. The mean birth weight of cases (±SD) was 3103(±547) g and that of controls 2624(±803) g; p=0.001. The mean gestational age of neonates with MAS was 39.2(±1.8) weeks and 36.2(±3.4) weeks for controls; p=0.001.

Maternal Characteristics

Table 1 compares maternal characteristics of the control group and neonates with MAS. Majority of neonates with MAS were born at a health care facility (288/290, 99% vs. 290/302, 96%; p=0.001). The presence of chorioamnionitis was not increased in neonates with MAS when compared with the control population (4/266, 1.5% vs. 9/287, 3.1%; p=0.206). Multigravidae pregnancies were less common in neonates with MAS when compared to the control population (3/287, 1% vs. 24/282, 8.5%; p=0.001). There were no significant differences in other maternal characteristics between groups.

Infant characteristics

Differences between neonates with MAS and the control group are also depicted in Table 1. More neonates born with MAS were born SGA when compared to the control group (74/301, 24.6% vs. 57/300, 19%; p=0.001). Substantially more neonates with MAS required resuscitation at birth when compared to the control population (107/304, 35.2% vs. 66/303, 21.8%; p=0.001). There were more MAS neonates with poor Apgar scores when compared with the control population (75/292, 25.7% vs. 43/288, 14.9%; p=0.001).

There was a seven-fold increase in the use of inotropes in neonates with MAS when compared to the control group (22/304, 7.2% vs. 2/304, 0.7%; p=0.001). There were significantly more neonates with MAS who required ventilation when compared to the control group (109/304, 35.9% vs. 17/304, 5.6%; p=0.001). The use of surfactant was similar in both groups (54/288, 18.8% vs. 53/289, 18.3%; p=0.750).

Table 1: Maternal and Neonatal characteristics of cases and controls

Maternal factors	Neonates with MAS n (%)	Neonates without MAS n (%)	p-value
Antenatal care	262/285 (91.9)	266/296 (89.9)	0.471
Caesarean sections	141/282 (50.0)	152/282(53.9)	0.354
Maternal race			
Black	294/301 (97.7)	290/304 (95.4)	0.481
White	3/301 (1.0)	5/304 (1.6)	
Indian	1/301 (0.3)	2/304 (0.7)	
Coloured	3/301 (1.0)	7/304 (2.3)	
Place of Birth			
Inborn	211/290 (72.8)	255/302 (84.4)	0.001
BBA	2/290 (0.7)	12/302 (4.0)	
Outside healthcare facility	77/290 (26.6)	35/302 (11.6)	
Chorioamnionitis	4/266 (1.5)	9/287 (3.1)	0.206
Primigravida	95/254 (37.4)	92/287 (32.1)	0.200
Multiple Gestation	3/287 (1.0)	24/282 (8.5)	0.001
HIV	88/300 (29.3)	97/301 (32.2)	0.440
Neonatal factors	**Neonates with MAS n (%)**	**Neonates without MAS n (%)**	**p-value**
Male	177/304 (58.2)	182/304 (59.9)	0.680
Female	127/304 (41.8)	122/304 (40.1)	
Adequacy of growth			
LGA	7/301 (2.3)	28/300 (9.3)	
AGA	220/301 (73.1)	215/300 (71.7)	0.001
SGA	74/301 (24.6)	57/300 (19.0)	
Apgars at 5 min ≤ 6	75/292 (25.7)	43/288 (14.9)	0.001
Initial resuscitation	107/304 (35.2)	66/303 (21.8)	0.001
Inotropic support	22/304 (7.2)	2/304 (0.7)	0.001
Surfactant	54/288 (18.8)	53/289 (18.3)	0.750
CPAP only	41/304 (13.5)	53/304 (17.4)	0.178
Ventilation	109/304 (35.9)	17/304 (5.6)	<0.001

Outcomes and complications

Differences in outcomes and complications between neonates with MAS compared to controls are illustrated in Table 2. There was a considerable increase in overall mortality in neonates with MAS when compared to the controls (37/304, 12.2% vs. 8/304, 2.6%; p=0.001). Significantly more neonates with MAS died in the first 12 hours when compared to controls (10/304, 3.3% vs. 0/304, 0%; p=0.002).

Complications seen in neonates with MAS compared to the control group were pneumothoraces (7/304, 2.3% vs. 1/304, 0.3%; p=0.033), and PPHN (44/304, 14.5% vs. 3/304, 1.0%; p=0.001). There was a trend towards an increase in MAS neonates that developed HIE when compared to the control population (34/304, 11.2% vs. 21/304, 6.9%; p=0.066). There was a two-fold increase in the number of neonates with MAS that developed sepsis when compared to the control group (40/300, 13.3% vs. 23/304, 7.6%; p=0.020).

When all significant variables were entered into a regression model, it was concluded that neonates born with MAS were more likely to be SGA, have poor Apgar scores and to require ventilation (see Table 3).

Table 2: Differences in outcomes between cases and controls

Neonatal Outcomes	Neonates with MAS n (%)	Neonates without MAS n (%)	p-value
Died (within 12 hours of admission)	10/304 (3.3)	0/304 (0.0)	0.002
Overall deaths	37/304 (12.2)	8/304 (2.6)	0.001
Pneumothorax	7/304 (2.3)	1/304 (0.3)	0.033
HIE	34/304 (11.2)	21/304 (6.9)	0.066
PPHN	44/304 (14.5)	3/304 (1.0)	0.001
Overall sepsis	40/300 (13.3)	23/304 (7.6)	0.020

Table 3: Binary logistic regression analysis for factors associated with MAS

Variables	Adjusted Odds Ratio (95%CI)	p-value
SGA	9.5 (3.191-28.218)	0.001
Multiple gestation	0.127 (0.035-0.462)	0.002
Ventilation	11.46 (6.050-21.708)	0.001
Apgars ≤6	1.947 (1.212-3.130)	0.006

Characteristics of survivors vs. non-survivors in neonates with MAS

On univariate analysis of neonates with MAS, factors associated with an increased mortality were poor five min Apgar scores (20/36, 55.6% vs. 55/255, 21.6%; p=0.001), the use of ventilatory support (25/37, 67.6% vs. 84/266, 31.6%; p=0.001), the need for inotropes (12/37, 32.4% vs. 10/266, 3.8%; p=0.001), the development of PPHN (18/37, 48.6% vs. 26/266, 9.8%; p=0.001) and HIE (13/37, 35.1% vs. 21/266, 7.9%; p=0.001). There was no association between mean birth weight or gestational age and chance of survival.

The use of surfactant in this study was associated with an increase in mortality in neonates with MAS when compared to the control group (13/35, 37.1% vs. 40/252, 15.9%; p=0.002). See Table 4.

On regression analysis, predictors of mortality in neonates with MAS were all stages of HIE (p=0.001), PPHN (p=0.001) and the use of inotropic support (p=0.001). See Table 5.

Table 4: Comparison between survivors and non-survivors in neonates with MAS

Variables	Non-survivors	Survivors	p-value
Apgar score at 5 min ≤6, n (%)	20/36 (55.6)	55/255 (21.6)	0.001
Maternal HIV positive	9/36 (25)	79/263 (30)	0.534
Resus in delivery room	16/37(43.2)	90/266 (33.8)	0.261
Ventilation	25/37 (67.6)	84/266 (31.6)	0.001
Use of inotropes	12/37 (32.4)	10/266 (3.8)	0.001
Surfactant	13/35 (37.1)	40/252 (15.9)	0.002
Complications			
PPHN	18/37 (48.6)	26/266 (9.8)	0.001
Pneumothorax	2/37 (5.4)	5/266 (1.9)	0.181
HIE	13/37 (35.1)	21/266 (7.9)	0.001

Table 5: Binary logistic regression analysis for predictors of mortality

Variables	Adjusted Odds Ratio (95%CI)	p -value
HIE	15.88 (5.59 - 45.09)	0.001
Use of inotropes	8.61 (2.56 – 28.93)	0.001
PPHN	8.67 (3.06 – 24.58)	0.001

4.0 DISCUSSION

Meconium aspiration syndrome remains a challenging condition in South Africa and other LMIC and is associated with a high mortality in newborns. The current study illustrates that despite adjunct therapies, MAS and its complications still remains a significant problem, with an overall incidence of 7.6%.

In this study, the overall mortality rate of neonates that developed MAS, was 12.2%. The reason for an increased percentage of deaths in the MAS group within 12 hours of admission is likely a result of severity of disease. There is a scarcity in evidence with regards to mortality rates secondary to MAS in LMIC. We cannot therefore ascertain whether there has been an overall decline in mortality. Mortality rates in MAS neonates as reported in a study by Velaphi et al are as high as 33%, however this study was based on ventilated neonates with MAS.[9] Sixty-eight percent of neonates with MAS that were ventilated in our study succumbed to illness. These elevated figures may be related to disease severity or they may reflect different approaches between the units.

It is evident that in this study, neonates that developed MAS were more likely to be term/post-dates. There were a large proportion of neonates with MAS who were SGA when compared to the control group. The association between MAS and SGA has been described in other studies and is likely due to prolonged intrauterine asphyxia.[13] The literature consistently states an association between the presence of chorioamnionitis and MAS, however this was not illustrated in the current study. This could be due to an under reporting of infections in maternal antenatal notes.[2, 17] There is a reported association between HIV infected mothers and MAS neonates but again this association was not illustrated in our study.[17]

It is no surprise that the current study demonstrates that neonates with MAS have significantly lower five-minute Apgar scores, often need resuscitation and develop severe respiratory distress or PPHN requiring ventilation and inotropic support. These variables are all independent predictors of mortality and correlate with findings in former studies.[13]

Although HIE did not prove to be directly associated with MAS, there was a trend towards an increase in all stages of HIE in MAS neonates. Ballot et al suggested that neonates who develop PPHN from MAS generally do not develop HIE as a consequence of reperfusion injury. This may be due to the fact that there is reperfusion with arterial blood of much lower oxygen content and thus protective against a compromised brain.[18] Neonates with PPHN may therefore be protected from HIE.

The number of pneumothoraces in both the MAS group and control population was very low. The incidence of pneumothoraces in our neonatal unit in the very low birth weight population of neonates has been reported at 0.9%. This might be as a result of ventilation techniques or the fact that there is a low threshold to ventilate neonates with MAS using HFOV. Some researchers have reported that HFOV reduces barotrauma and prevents air leak syndromes however there is conflicting evidence in animal and clinical models.[19]

Surfactant is known to improve oxygenation, decrease disease severity and the need for ECMO, which we do not offer in our unit.[10, 19] In the current study, however, there was no improvement in mortality profile in those who received surfactant and in fact surfactant therapy was associated with an increase in mortality. The high mortality rate was likely as a result of disease severity in neonates with MAS. In the current study, the use of surfactant in neonates with MAS was similar to that in the control group. This most likely reflects the higher number of preterm infants in the control group as all neonates with hyaline membrane disease receive surfactant replacement therapy.

Persistent pulmonary hypertension is a common complication in neonates born with MAS. Fourteen and a half percent of neonates that were diagnosed with MAS

developed PPHN, a condition that carries a high mortality.[9, 19] Inhaled nitric oxide is an ideal agent in these neonates as it causes pulmonary vasodilatation and decreases ventilation-perfusion mismatching, improving oxygenation. There are however 30-50% of neonates with MAS that will not respond to iNO therapy. Inhaled nitric oxide was not available in the neonatal unit at the time of this study.

The number of neonates with MAS that developed sepsis was almost double that of the control group. Organisms isolated from positive blood cultures included Staphylococcus epidermidis, Streptococcus viridans, Streptococcus agalactiae and Staphylococcus aureus. This contributed to overall mortality and is likely as a result of prolonged hospital stay in neonates with MAS when compared to the control group. There is little information regarding the association between MAS and sepsis and so it was difficult to make a comparison.

5.0 LIMITATIONS

The retrospective nature of this study is a limitation as not all records were complete and there was some information missing. The role of intratracheal suctioning of neonates in labour ward to prevent MAS could not be evaluated. This could be a topic for further research.

6.0 CONCLUSION

This study illustrates that neonates born with MAS have suffered some element of intrauterine stress and are often born SGA. Neonates with MAS have poor five-minute Apgar scores and a large proportion of them require ventilation for severe respiratory distress or PPHN. Hypoxic ischaemic encephalopathy, PPHN and the use of inotropes are predictors of mortality in the MAS neonate in our neonatal unit. The use of surfactant, despite supporting evidence for its use in MAS, has not shown to decrease the mortality profile in our unit.

Once meconium has crossed the vocal cords and reached the lung parenchyma, it becomes difficult to prevent MAS. Meconium aspiration syndrome is part of a

spectrum of perinatal asphyxia and requires a combined Obstetric and Paediatric approach in order to decrease overall mortality rates.

7.0 REFERENCES

1. Lee J, Romero R, Lee KA, Kim EN, Korzeniewski SJ, Chaemsaithong P, et al. Meconium aspiration syndrome: a role for fetal systemic inflammation. American journal of obstetrics and gynecology. 2016;214(3):366 e1-9.
2. Dargaville PA, Copnell B, Australian, New Zealand Neonatal N. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies, and outcome. Pediatrics. 2006;117(5):1712-21.
3. Wiswell TE. Delivery room management of the meconium-stained newborn. Journal of perinatology : official journal of the California Perinatal Association. 2008;28 Suppl 3:S19-26.
4. Meerkov M, Weiner G. Management of the Meconium-Stained Newborn. Division of Neonatal-Perinatal Medicine. 2016;17(8):e471-e7.
5. Wiswell TE, Tuggle JM, Turner BS. Meconium aspiration syndrome: have we made a difference? Pediatrics. 1990;85(5):715-21.
6. Bhat R, Vidyasagar D. Delivery room management of meconium-stained infant. Clinics in perinatology. 2012;39(4):817-31.
7. Whitfield JM, Charsha DS, Chiruvolu A. Prevention of meconium aspiration syndrome: an update and the Baylor experience. Proceedings. 2009;22(2):128-31.
8. Yoder BA, Kirsch EA, Barth WH, Gordon MC. Changing obstetric practices associated with decreasing incidence of meconium aspiration syndrome. Obstetrics and gynecology. 2002;99(5 Pt 1):731-9.
9. Velaphi S, Van Kwawegen A. Meconium aspiration syndrome requiring assisted ventilation: perspective in a setting with limited resources. Journal of perinatology : official journal of the California Perinatal Association. 2008;28 Suppl 3:S36-42.
10. Dargaville PA, Mills JF. Surfactant therapy for meconium aspiration syndrome: current status. Drugs. 2005;65(18):2569-91.
11. Wiswell TE, Gannon CM, Jacob J, Goldsmith L, Szyld E, Weiss K, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. Pediatrics. 2000;105(1 Pt 1):1-7.

12. Network VO. Manual of Operations: Part 2, Data Definitions and Infant Data Forms 2016 [Available from: public.vtoxford.org/wp-content/uploads/2015/09/Manual_of_Operations_Part2_v20.pdf.
13. Louis D, Sundaram V, Mukhopadhyay K, Dutta S, Kumar P. Predictors of mortality in neonates with meconium aspiration syndrome. Indian pediatrics. 2014;51(8):637-40.
14. Ballot DE, Cooper PA, Davies VA, P.Chirwa, Ramdin T. Neonatal Protocols CMJAH. 2015:15.
15. Jardine C, Ballot DE. The use of nasal CPAP at Charlotte Maxeke Johannesburg Academic Hospital. SAJCH. 2015;9(2):45-8.
16. Beck-Arnold E, Chirwa P, Diar H, Mackay C, Mathivha K, Mokhachane M, et al. Neonatal Protocols. Chris Hani Baragwanath Hospital.2012. 30 - 157 p.
17. Gupta SK, Haerr P, David R, Rastogi A, Pyati S. Meconium aspiration syndrome in infants of HIV-positive women: a case-control study. Journal of perinatal medicine. 2016;44(4):469-75.
18. Ballot DE, Rothberg AD, Davies VA, Smith J, Kirsten G. Does hypoxemia prevent brain damage in birth asphyxia? Medical hypotheses. 1993;41(4):344-7.
19. Chettri S, Bhat BV, Adhisivam B. Current Concepts in the Management of Meconium Aspiration Syndrome. Indian journal of pediatrics. 2016.

APPENDICES

Appendix A: Research Protocol

A case-control review of neonates with meconium aspiration syndrome admitted to a tertiary hospital in Johannesburg, South Africa

---

INVESTIGATOR: Lara Jones MBChB (Wits)
STUDENT NUMBER: 0200983G
DEGREE: MMED (Paediatrics)

SUPERVISOR:
Professor Daynia Ballot
MBChB (Wits), FCPaed (SA), PhD
Paediatric Neonatologist Charlotte Maxeke Johannesburg
Academic Hospital

CORRECTIONS TO PROTOCOL

Page 1: Title: 'retrospective review' changed to 'case-control'. Deletion of 'between January 2013 and December 2015'. 'South Africa' inserted after 'Johannesburg'.

Page 6: Aim: Line 2, the following was added; 'and compare them to neonates without MAS to identify risk factors and isolate predictors of mortality'.

Page 6: Objectives: Insertion of new objectives. 'a. To describe the clinical characteristics of neonates born at CMJAH with MAS and without MAS.' 'b. To compare clinical characteristics between the case and control individuals to isolate risk factors and predictors of mortality'. Point c, 'discuss' changed to 'determine'.

Page 6: Definitions: Point 2. Meconium aspiration syndrome definition changed to ' respiratory distress in a meconium exposed neonate that develops within 1 hour of birth with a pa02< 50mmHg in room air, central cyanosis in room air or supplemental oxygen to maintain a pa02 >50mmHg'.

Page 7: Inserted definition 6, 'Early onset sepsis – sepsis before day 3 of life'.

Page 7: Study design: Whole paragraph changed to 'It will be a case control study comparing neonates with MAS and neonates without MAS. The study will review an existing database of all neonates admitted to CMJAH Prem Unit and NICU from 1 January 2013 – 30 April 2015'.

Page 7: Sample population: Study period changed from '1 January 2013 – 31 December 2015' to ' 1 January 2013 - 30 April 2015'.
Page 7: Inclusion criteria: 'with MAS' omitted from sentence. Exclusion criteria: point inserted; 'Neonates with major congenital abnormalities and surgical conditions'.

Page 7: Procedures/Data collection: 'Meconium aspiration syndrome' omitted and study period changed from '1 January 2013 – 31 December 2015' to '1 January 2013 – 30 April 2015'.

Page 8: Data analysis. Whole paragraph deleted from 'Continuous variables will be compared using student's t-test or Mann Whitney U analysis, as appropriate'. Insertion of paragraph, 'Bivariate analysis will be performed using Chi-Square tests of homogeneity to determine if there is a statistically significant difference in frequencies between cases and controls. Differences in means across cases and controls for normally distributed continuous variables will be compared using two sample t-tests. We will do binary logistic regression to isolate variables associated with MAS as well as risk factors associated with mortality in the MAS group'.

Page 8: Sample size: Line 1, '250' changed to '325'. 'Control' inserted before 'sample size' in line 2. '225' changed to '300'. Sentence inserted, 'There will be an equal number of cases and controls'.

1. Introduction – Background Information

Meconium aspiration syndrome (MAS) is an important cause of mortality and respiratory morbidity in the term and post term infant.(1,2) Approximately 3 to 4% of neonates born with meconium stained liquor will develop MAS.(3)

Meconium Aspiration Syndrome is defined as respiratory distress in a meconium exposed neonate that develops within 1 hour of birth with a PaO2 <50mmHg in room air, central cyanosis in room air or supplemental oxygen to maintain a PaO2 >50mmHg.(4) These clinical findings should be accompanied by an abnormal chest radiograph showing non-homogenous infiltrates, with areas of diminished aeration with or without hyperinflation.(5) Some important risk factors associated with the presence of meconium stained amniotic fluid and thus an increase in the development of MAS, include fetal compromise, which is indicated by pathological fetal heart rates, abnormal cardiotocographs and, or low Apgar scores. Post maturity, maternal toxaemia and prolonged labour with subsequent necessity for Caesarean sections are also associated with a higher risk of MAS.(2, 6, 7)

Meconium Aspiration Syndrome causes diffuse inflammation of the lung parenchyma resulting in an associated meconium-induced pneumonitis. Meconium has a thick, particulate consistency causing complete or partial airway obstruction, which further complicates the disease process. The combination of these two processes can cause severe respiratory failure with or without pulmonary hypertension, as well as air leak syndromes.(8) Those neonates that demonstrate hypoxaemic respiratory failure often develop a respiratory acidosis and, or pulmonary hypertension.

The incidence of MAS in developed countries has decreased steadily over the last 15 years from 5% to 2%.(7) There has been a significant decline in the mortality rate from MAS over the years in the developed world.(6) Mortality rates ranged from 28 to 40% in studies from the 1970s and 1980s to less than 15% in recent literature.(9) The decrease in mortality is attributed to the improvement in obstetric practices (earlier intervention when fetal distress is noted and avoidance of post term deliveries).(9) The use of respiratory adjuncts, namely surfactant, nitric oxide and

high frequency ventilation has decreased the mortality rate in neonates with MAS, but has not made an impact on duration of mechanical ventilation and oxygen therapy.(2)

At least one third of neonates presenting with MAS require intubation and mechanical ventilation.(2) Mechanical ventilation is still associated with a high morbidity and mortality in low-middle income countries (LMIC). This is attributed to the fact that there are often delays in instituting treatment, there is limited access to adjunct respiratory therapies and patients frequently have concomitant infections.(10)

Common complications associated with MAS are persistent pulmonary hypertension, pulmonary air leaks and pneumonia.(10) Management of these neonates remains problematic and a significant challenge especially in LMIC where adjunctive respiratory therapies and ICU beds are not freely available.(11)

There is still much controversy regarding the effectiveness of postpartum intubation and suctioning in the prevention of MAS. Suctioning the nasopharynx with delivery of the head and endotracheal suctioning has not been associated with a decrease in respiratory distress in vigorous meconium exposed neonates when compared with expectant management.(12) Although tracheal suctioning has been suggested to improve the clinical course of MAS in non vigorous meconium exposed neonates, no therapies to date have been definitively proven to be effective.(3) It is most probable that MAS is an antepartum event and cannot be prevented by post partum suctioning of the neonate's airway.

Meconium Aspiration Syndrome, still remains a leading cause of mortality in LMIC, including South Africa, due to our limited access to resources.(10)

Justification for the study

Meconium Aspiration Syndrome is an important cause of morbidity and mortality in otherwise healthy term and post term infants. The aim of this study is to look at the clinical profile of MAS, identify associated risk factors and isolate predictors of mortality. Earlier recognition of neonates at highest risk for meconium aspiration

syndrome can allow more timely institution of effective therapies. The study will highlight the current treatment practices of meconium exposed neonates in LMIC and subsequent outcomes when different treatment modalities are used. Increased awareness when assessing neonates born with MAS and offering improved neonatal care with modalities such as exogenous surfactant may decrease the incidence of MAS and subsequent need for ventilation. This in turn will decrease the burden where resources are limited.

One will never be able to completely eliminate the incidence of MAS however with the advent of improved neonatal practices, we may be able to decrease it significantly.

2. Aim

To review neonates born with Meconium Aspiration Syndrome admitted to the Charlotte Maxeke Johannesburg Hospital Prem Unit and Neonatal ICU and compare them to neonates without MAS to identify risk factors and isolate predictors of mortality.

3. Objectives

a. To describe the clinical characteristics of neonates born at CMJAH with MAS and without MAS.

b. To compare clinical characteristics between the case and control individuals to isolate risk factors and predictors of mortality.

c. To determine treatment, complications and outcomes of these patients.

4. Definitions

1. Neonate – a child presenting within the first 28 days of life
2. Meconium aspiration syndrome– respiratory distress in a meconium exposed neonate that develops within 1 hour of birth with a pa02< 50mmHg in room air, central cyanosis in room air or supplemental oxygen to maintain a pa02 >50mmHg.
3. Survanta – modified bovine surfactant extract

4. IPPV – conventional mode of ventilation.
5. HFOV – Type of mechanical ventilation that uses a respiratory rate greater than 4 times the normal value and very small tidal volumes
6. Early onset sepsis – sepsis before day 3 of life

5. Methods

a. Study Design

It will be a case control study comparing neonates with MAS and neonates without MAS. The study will review an existing database of all neonates admitted to CMJAH Prem Unit and NICU from 1 January 2013 – 30 April 2015.

b. Sample Population

The sample population includes all neonates admitted to CMJAH NICU and Prem Unit from 1 January 2013 – 31 December 2015.

i. Inclusion Criteria

Neonates admitted to CMJAH Prem Unit and NICU during the study period.

ii. Exclusion Criteria

Neonates with missing records.

Neonates less than 1500 grams

Neonates with major congenital abnormalities and surgical conditions

c. Procedures/ Data Collection

The neonatal database at CMJAH will be reviewed to identify all neonates who were admitted to NICU and Prem Unit from 1 January 2013 – 30 April 2015. Discharge (including deaths) information is captured for all neonates admitted to CMJAH Prem Unit and NICU on a computerized database. Data is managed using Research Electronic Data Capture (REDCap), which is hosted by University of Witwatersrand. The data will be collected and entered onto a prepared data sheet (appendix A). The data sheet will capture demographic information (Maternal age, parity, infants'

gestational age, birth weight and gender), mode of delivery – if assisted or Caesarean, indication stated. The data sheet will also state if any resuscitative measures were required at delivery and what the subsequent Apgar scores at 1/5/10 minutes were. The management of these patients will be captured in terms of oxygen therapy, need for IPPV or HFOV and surfactant. The outcomes of patients will be documented. This will include PPHN, death, pneumothoraces, late onset sepsis and ultimately discharge home.

d. Data Analysis

Data will be described using standard statistical methods. Continuous variables will be described using measures of central tendency – mean and standard deviation for those variables with a normal distribution and median and range for those variables with a skewed distribution. Categorical variables will be described using frequencies and percentages. Variables will be compared between survivors and non-survivors. Bivariate analysis will be performed using Chi-Square tests of homogeneity to determine if there is a statistically significant difference in frequencies between cases and controls. Differences in means across cases and controls for normally distributed continuous variables will be compared using two sample t-tests. We will do binary logistic regression to isolate variables associated with MAS as well as risk factors associated with mortality in the MAS group'.

e. Sample Size

There are more than 325 neonates with a diagnosis of MAS on the existing database, so it is estimated that the case sample size will contain at least 300 neonates. There will be an equal number of cases and controls.

6. Significance

The findings of this study will be shared with both obstetric and neonatal teams to highlight any strategies which could be put in place to first of all act earlier on term and post term fetus's with fetal distress (as this carries a higher likelihood of presence of meconium stained liquor) and secondly to alert the paediatricians to possible management strategies once the infant is delivered or starts decompensating

postnatally. Many meconium aspiration syndrome babies initially present with mild respiratory distress and can be mistaken as a TTN only to discover worsening respiratory distress, hyperinflation and hypoxia which later ensues.

7. Limitations

The study is a retrospective audit of an existing database. Some data is missing and not all records are complete. In particular, there is no record of whether or not the neonate was intubated and suctioned for meconium stained liquor. The study also doesn't take into account neonates with Meconium Aspiration Syndrome that are born with IUGR and may weigh less than 1500g.

8. Ethical Considerations

The proposal for this study will be submitted to the University of Witwatersrand Protocol Review Committee and Human Research Ethics Committee (HREC) of the University of Witwatersrand for approval. As this is a retrospective audit, no consent will need to be obtained from individual patients. Data sheets will only contain a study number. The patient's name, hospital number and date of birth will be stored on a separate database at a different, secure location so that only the investigator and the supervisors will have access to this information. The study has been granted ethics clearance (certificate number: M160571).

9. Timeline

	Feb 2016	Mar 2016	Apr 2016	May 2016	Jun 2016	July 2016	Aug 2016	Sept2 016	Oct 2016	Nov 2016	Dec 2016	Jan 2017	Feb 2017
Literature review													
Protocol preparation													
Protocol assessment													
Ethics approval													
Post-grad approval													
Data collection													
Data analysis													
Write-up report													
Write-up paper													

10. Cost/Funding

The cost involved in the study is for stationery, printing and binding. It is estimated that the cost will be R300. This cost will be borne by the investigator, as there is no funding for this study.

11. References

1. Lee J, Romero R, Lee KA, Kim EN, Korzeniewski SJ, Chaemsaithong P, et al. Meconium aspiration syndrome: a role for fetal systemic inflammation. American journal of obstetrics and gynecology. 2016;214(3):366 e1-9.
2. Dargaville PA, Copnell B, Australian, New Zealand Neonatal N. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies, and outcome. Pediatrics. 2006;117(5):1712-21.
3. Wiswell TE. Delivery room management of the meconium-stained newborn. Journal of perinatology : official journal of the California Perinatal Association. 2008;28 Suppl 3:S19-26.
4. Vermont Oxford Network 2015 [24 April 2016]. Available from: https://public.vtoxford.org.
5. Louis D, Sundaram V, Mukhopadhyay K, Dutta S, Kumar P. Predictors of mortality in neonates with meconium aspiration syndrome. Indian pediatrics. 2014;51(8):637-40.
6. Wiswell TE, Tuggle JM, Turner BS. Meconium aspiration syndrome: have we made a difference? Pediatrics. 1990;85(5):715-21.
7. Bhat R, Vidyasagar D. Delivery room management of meconium-stained infant. Clinics in perinatology. 2012;39(4):817-31.
8. Whitfield JM, Charsha DS, Chiruvolu A. Prevention of meconium aspiration syndrome: an update and the Baylor experience. Proceedings. 2009;22(2):128-31.
9. Yoder BA, Kirsch EA, Barth WH, Gordon MC. Changing obstetric practices associated with decreasing incidence of meconium aspiration syndrome. Obstetrics and gynecology. 2002;99(5 Pt 1):731-9.
10. Velaphi S, Van Kwawegen A. Meconium aspiration syndrome requiring assisted ventilation: perspective in a setting with limited resources. Journal of perinatology : official journal of the California Perinatal Association. 2008;28 Suppl 3:S36-42.
11. Dargaville PA, Mills JF. Surfactant therapy for meconium aspiration syndrome: current status. Drugs. 2005;65(18):2569-91.
12. Wiswell TE, Gannon CM, Jacob J, Goldsmith L, Szyld E, Weiss K, et al. Delivery room management of the apparently vigorous meconium-stained neonate:

results of the multicenter, international collaborative trial. Pediatrics. 2000;105(1 Pt 1):1-7.

12. Data Collection Sheet

Study number:

Maternal details:

Age

Parity

Gravidity

Evidence of chorioamnionitis

Delivery Details:

Mode of Delivery, and reason for c/s if indicated

Age on admission

Apgars

Birth Weight

Place of Birth: Inborn

At another hospital

BBA

Born at MOU

Neonatal details:

Gestational age

AGA/ SGA

Gender

Initial resuscitation in delivery room

Early onset sepsis

Respiratory Support

Oxygen

IPPV

HFOV

Surfactant therapy

Outcomes

Died /Discharged

Duration of admission

Duration of ventilation

Pneumothoraces

PPHN

Late onset sepsis

Chronic lung disease (oxygen at 28 days of life)

Home oxygen

Appendix B: Ethics clearance certificate

R14/49 Dr Lara Alexandra Jones

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160571

NAME: (Principal Investigator)	Dr Lara Alexandra Jones
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Retrospective Review of Neonates with Meconium Aspiration Syndrome Admitted to a Tertiary Hospital in Johannesburg between January 2013 and December 2015
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	16/09/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year.

Principal Investigator Signature

Date 24/01/2019

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Author guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

To access and submit an article already in production, please see the guidelines here.

Author Guidelines
Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude

publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAJCH* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has

given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAJCH.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The Agreement form should be uploaded along with other submissions files and any submission will be considered incomplete without it *[forthcoming].*

Material submitted for publication in the *SAJCH* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAJCH* does not hold itself responsible for statements made by the authors. The corresponding author should also indicate if the research forms part of a postgraduate short report, dissertation or thesis.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAJCH* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to any third party without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAJCH* or its publisher HMPG on matters relating to the journal

or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAJCH* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:

- **Background:** why the study is being done and how it relates to other published work.
- **Objectives:** what the study intends to find out
- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman

WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:
  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
- Provincial Gazettes:
  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
- Acts:
  South Africa. National Health Act No. 61 of 2003.
- Regulations to an Act:
  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
- Bills:
  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
- Green/white papers:
  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
- Case law:
  Rex v Jopp and Another 1949 (4) SA 11 (N)
  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard)
  (4): Volume number
  SA: SA Law Reports
  11: Page or section number
  (N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
  NOTE: no . after the v
- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source

person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *SAJCH* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form [forthcoming]
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
  - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

Article Processing Charges

There is currently no article-processing charge (APC), also known as page fees, for the publication of manuscripts.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is currently applicable. Queries can be directed to Dianes@hmpg.co.za or Claudian@hmpg.co.za

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors

- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.
Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

Published articles are covered by the following major indexing services. As such articles published in the *SAJCH* are immediately available to all users of these databases, guaranteed a global and African audience:

- DOAJ
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

- EBSCO
- EMBASE

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Copyright Notice

Appendix D: Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

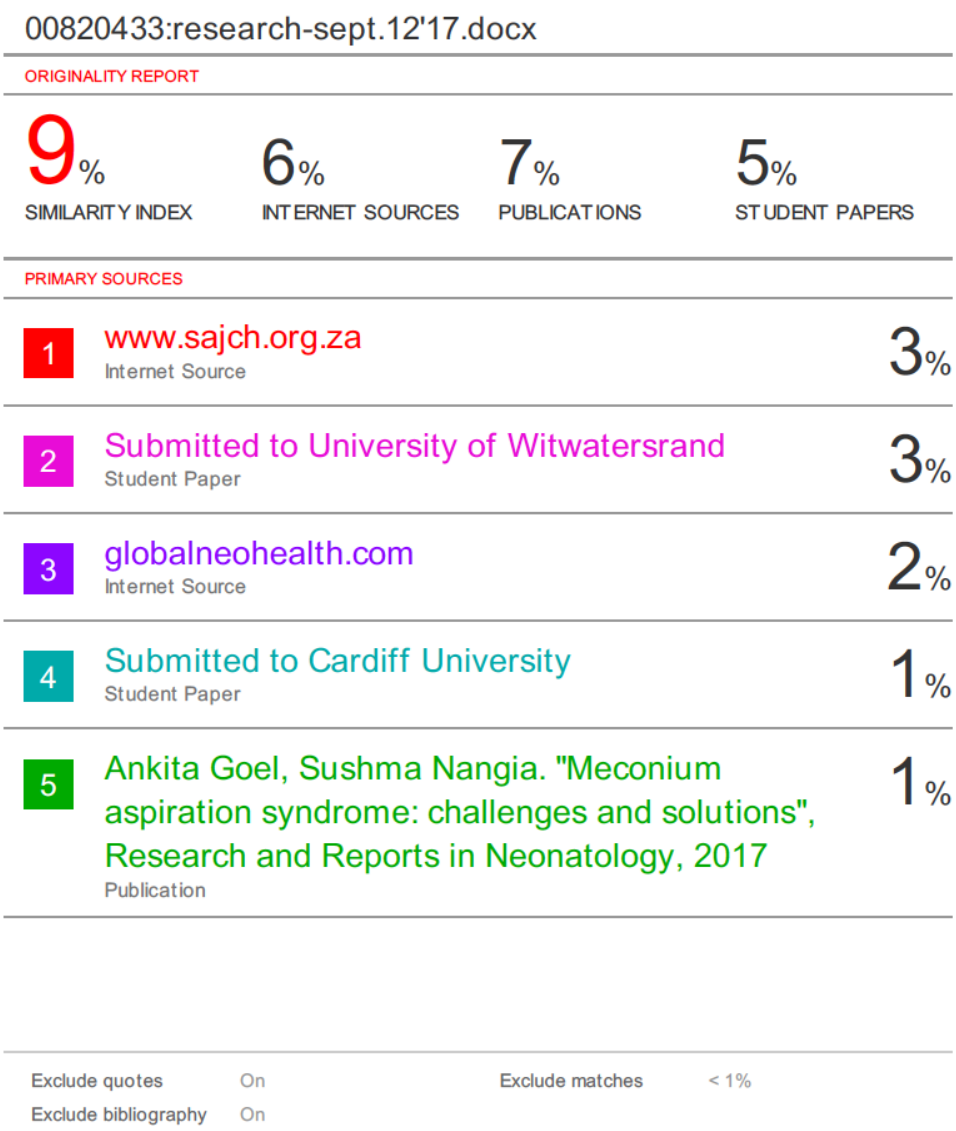
I Lara Alexandra Jones (Student number: 0200983G) am a student registered for the degree of MMed (Paeds) in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 24/01/2019

Appendix E: Turnitin Report



00820433:research-sept.12'17.docx

ORIGINALITY REPORT

9%	6%	7%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.sajch.org.za Internet Source	3%
2	Submitted to University of Witwatersrand Student Paper	3%
3	globalneohealth.com Internet Source	2%
4	Submitted to Cardiff University Student Paper	1%
5	Ankita Goel, Sushma Nangia. "Meconium aspiration syndrome: challenges and solutions", Research and Reports in Neonatology, 2017 Publication	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		