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* Nielsen RMS data for the Diapering Bedwetting category, period ending December 2020.

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CASE REPORT

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South Africa regains polio-free status: Processes involved and lessons learnt

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The World Health Organization recommends continuous immunisation coverage and polio surveillance standards for countries to sustain a polio-free status. We highlight experiences and lessons learnt by South Africa (SA) in losing – and subsequently regaining – its polio-free status. Following some decline in achieving acute flaccid paralysis surveillance and immunisation coverage targets, SA had its polio-free status withdrawn in 2017. Existing gaps were addressed and the polio-free status was regained in 2019. Lessons learnt from this experience include reaffirming the importance of continued commitment to polio eradication efforts, strengthening health systems through quality improvement projects, ensuring accountability in supervision, and monitoring of polio-related indicators. Consistent political commitment, collaboration and accountability are critical in sustaining the country's health programmes, including maintaining a polio-free status and closing identified gaps.

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Poliovirus is the main infectious cause of disability worldwide, with millions of children disabled globally, including in Africa.[1] Poliomyelitis is preventable through effective vaccination coverage, which has existed for decades.[2] Efforts across the world to eradicate the disease have taught us several lessons so far.[3]

The key goal of the Global Polio Eradication Initiative (GPEI) in the new 2019 - 2023 Polio Endgame strategy is for countries to achieve polio-free certification.[4] For a country to be given a polio-free status by the World Health Organization (WHO), it needs to achieve the following minimum targets: >80% oral poliovirus vaccine (OPV) immunisation coverage; maximum 2/100 000 cases of non-polio acute flaccid paralysis (AFP) in the population younger than 15 years old per year; and >80% stool adequacy rate for reported AFP cases.[5] By 2017, Nigeria was the only African country where poliovirus remained endemic;[6] in 2020, it was declared to be polio free. This led to regional polio certification, which was a remarkable and significant achievement and a testament to the commitment of key partners in providing the much-needed resources and better implementation of strategies.[7]

To retain certification, a country with polio-free status is expected to maintain a sensitive AFP surveillance system with a robust poliovirus outbreak preparedness and response plan and a high population immunisation coverage against the virus, as well as robust containment activities.[5] In Africa, this is monitored by an independent body of experts, namely the African Region Certifications Committee (ARCC), who review annual progress reports from the various national certification committees.[8] The ARCC reserves the right to withdraw or rescind a country's polio-free status if the country's performance is suboptimal.[9] South Africa (SA) is the only country in the African region that has lost – but subsequently regained – its polio-free status owing to suboptimal performance in maintaining the outlined WHO standards.[10] In this report, we describe the SA experience and the lessons learnt.

Withdrawal of South Africa's polio-free status

SA had its last wild polio case in 1989 and received the initial polio-free status in 2006,[10,11] with annual progress reports submitted to the ARCC from then on. Between 2015 and 2017, a constant decline was reported in full poliovirus immunisation coverage (based on administration of the third dose of either the inactivated polio vaccine (IPV) or the OPV, with the lowest performance at 72.5% in 2016. This was lower than the national target of 80% and occurred at the time of a global shortage of the hexavalent vaccine.[12] During this period, there was generally a low immunisation coverage, which resulted in low population immunity in SA, leading to outbreaks of other vaccine-preventable diseases.[13] In addition, the country has reported suboptimal performance in stool adequacy rates since 2006, with a figure of 64.2% reported by 2017.[12]

The decline in immunisation coverage in SA between 2015 and 2017, especially of the OPV3/IPV3, indicated that the immunisation coverage levels for the country were not high enough to prevent imported wild poliovirus from circulating, with the possible re-emergence of poliomyelitis.[12] In addition, AFP surveillance and stool adequacy rates consistently below 80% reflected poor AFP case reporting and investigation, indicating that the surveillance system in SA was not sensitive and would be unable to detect poliovirus importation should it occur. The national certification committee raised these concerns in their annual ARCC progress reports and the country's polio-free status was consequently withdrawn in December 2017.[14]

How did South Africa regain its polio-free status?

SA realised the need to take action, address the gaps and change the situation. These were accomplished through putting in place measures such as polio eradication advocacy initiatives, strengthening

immunisation systems through quality improvement interventions, redefining polio eradication efforts, closely monitoring immunisation and polio surveillance, and improving collaborative efforts.

The country had two advocacy visits from the ARCC and the WHO African region. Meetings held with the national and provincial health ministers led to the health department officially committing to polio eradication efforts.[14] This involved a national advocacy memorandum to improve the polio surveillance indicators and a special appeal to prioritise polio eradication with a focus on the worst-performing provinces.[15] In addition, the national certification committee and other polio committee members used existing platforms, such as institutional academic meetings, to advocate for and support the process of addressing the existing gaps.

The national Department of Health's Expanded Programme on Immunisation (EPI) unit, with support from the national Maternal and Child Health Department and the WHO secretariat, conducted provincial workshops for maternal and child health managers and all involved in polio eradication services. These workshops focused on sensitising the provinces to the poor performance, identifying reasons for poor performance, and developing quality improvement plans at district and provincial level. Appropriate resources were subsequently allocated for provinces to meet their demands, which also strengthened their collaboration with the national health department and other partners such as the WHO country office, UNICEF and the National Institute for Communicable Diseases. Poor-performing provinces received individualised support from national and provincial managers and partners such as the WHO and UNICEF. Progress on implementation of quality improvement interventions at district level was presented quarterly and, in return, technical input was given to implementers. In addition, SA had rolled out the use of the integrated supportive supervision tool on the open data kit since April 2018. The open data kit has shown to improve surveillance recording[16] and since its implementation, most of the active-case search and surveillance supervision visits were documented.

It is important to ensure that poliovirus samples and infectious materials (including potentially infectious materials) in laboratories are handled according to the requirements of the Global Action Plan III to Minimise Poliovirus to prevent the virus from being reintroduced into the population and environment.[17] To this end, SA completed the process of laboratory surveys and documentation of the presence or absence of infectious and potentially infectious materials, with support from the WHO.

Environmental surveillance for poliovirus monitors the transmission of poliovirus among human populations by examining specimens in the environment that are contaminated by human faeces.[18] The ARCC recommended that SA establish an environmental surveillance programme, which was subsequently rolled out (in 2019) to three metropolitan areas, namely City of Ekurhuleni, City of Johannesburg and City of Tshwane. In addition, the country developed a polio outbreak preparedness and response plan in line with the WHO standard operating procedures for any polio outbreak or event, which resulted in two immune-deficient, vaccine-derived poliovirus cases successfully being detected, investigated and managed.[14]

Results

Collaborative efforts in addressing polio eradication gaps resulted in positive progress on various polio immunisation and surveillance indicators.

Polio immunisation coverage

An increase in polio immunisation coverage, exceeding the 80% target, was observed between 2016 and 2018 (Fig. 1).

Stool adequacy rate for reported cases of acute flaccid paralysis

Fig. 2 summarises the analysis of AFP surveillance data since SA was certified polio free. At a national level, SA has been performing below the 80% target for stool adequacy rate since 2007. The initiatives to regain the country's polio-free status have shown to improve the indicator, with the rate exceeding the 80% target for the first time in 2019. Even though the performance was

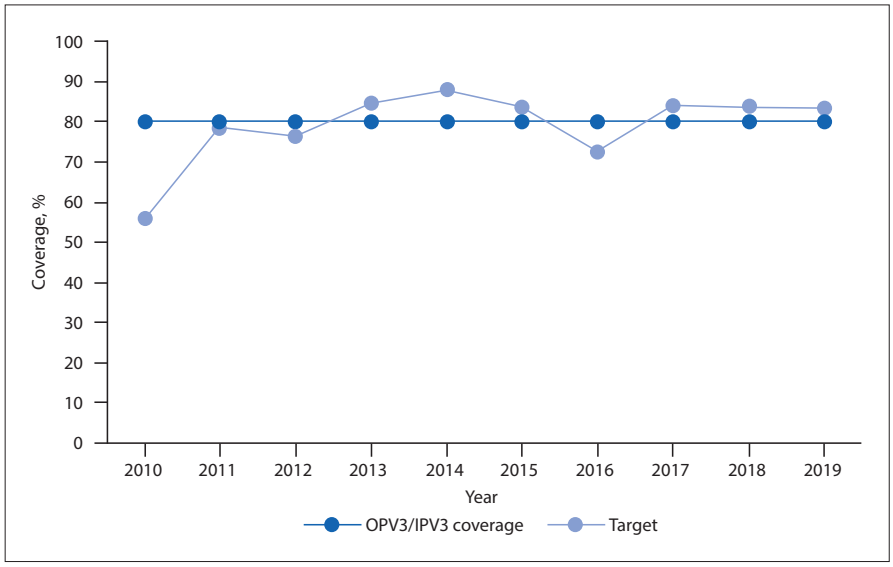

Fig. 1. Polio vaccine coverage in South Africa, 2010 - 2019. The target is shown as a solid line.

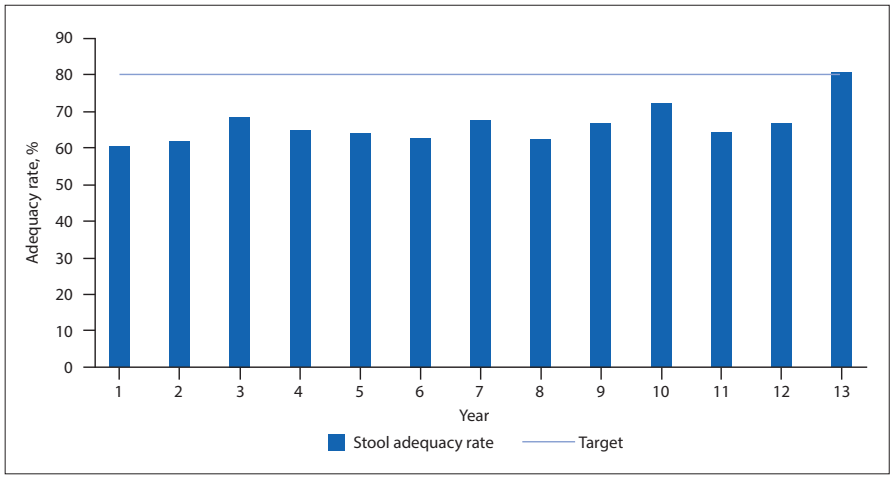

Fig. 2. Stool adequacy rate for reported cases of acute flaccid paralysis, 2007 - 2019. The target is shown as a solid line.

above target at national level, some provinces (Free State, Gauteng and the Western Cape) were still below target (Fig. 3).

Feedback on results

In addition to the 80% stool adequacy target, the National Institute for Communicable Diseases requires that 80% of all results be reported within 14 days of receipt from the laboratory. Gaps have existed since 2000 (Fig. 4).

Non-polio acute flaccid paralysis surveillance rate

Surveillance of non-polio AFP among children younger than 15 years reflects the sensitivity of the polio surveillance system. The WHO recommends that 2 cases per 100 000 of the population in this age group should be detected annually for a country to qualify for polio-free certification.[5] However, as SA has been performing above the minimum WHO standard, a higher benchmark was set by the country, namely 4 cases of non-polio AFP in 100 000 of the target population detected annually.

SA has consistently performed above the WHO target (except in 2007 and 2010), with the best performance in 2019 (Fig. 5). The intiatives put in place since 2017 have contributed to a steady improvement in surveillance performance.

National recommendation and documentation report

In response to the progress in the surveillance, immunisation coverage and containment indicators between 2017 and 2019, the national certification committee prepared a report to motivate for the certification of polio eradication in the country. In this report, the committee expressed confidence that the country was able to achieve and sustain routine immunisation and surveillance targets and recommended that the ARCC declare SA polio free. The report was followed by a verification visit by ARCC and WHO Africa representatives (see Fig. 6).

During the visit, the draft report was thoroughly reviewed and verified, which included facility visits to priority provinces, and feedback and recommendations were offered to address gaps. The final report was presented to the ARCC at a meeting held in Lusaka, Zambia, on 16 - 20 September 2019, where the regional committee accepted the SA recommendation and declared the country polio free. Further recommendations were included as part of the acceptance.[14]

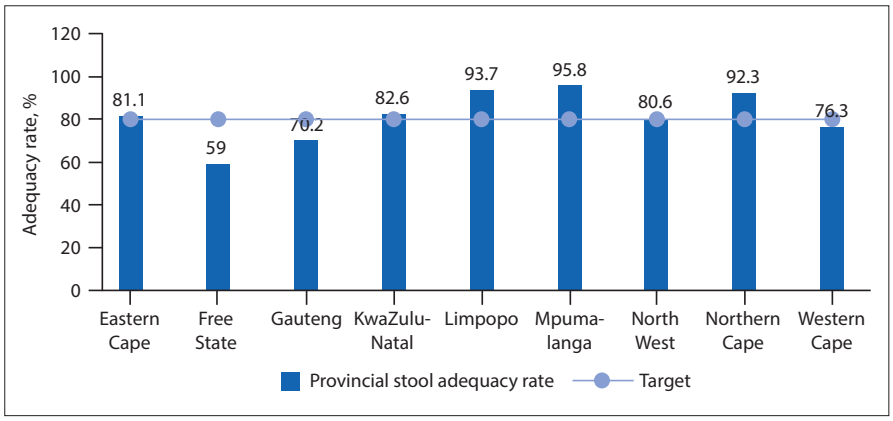

Fig. 3. Provincial surveillance of stool adequacy rate in 2019. The target is shown as a solid line.

Lessons learnt

Key lessons learnt from the SA experience are as follows:

1. Once polio-free status is achieved, continued effective leadership and commitment to polio eradication efforts are needed to ensure sustainability of polio surveillance.
2. Programmes shown to yield good results should be integrated to use resources

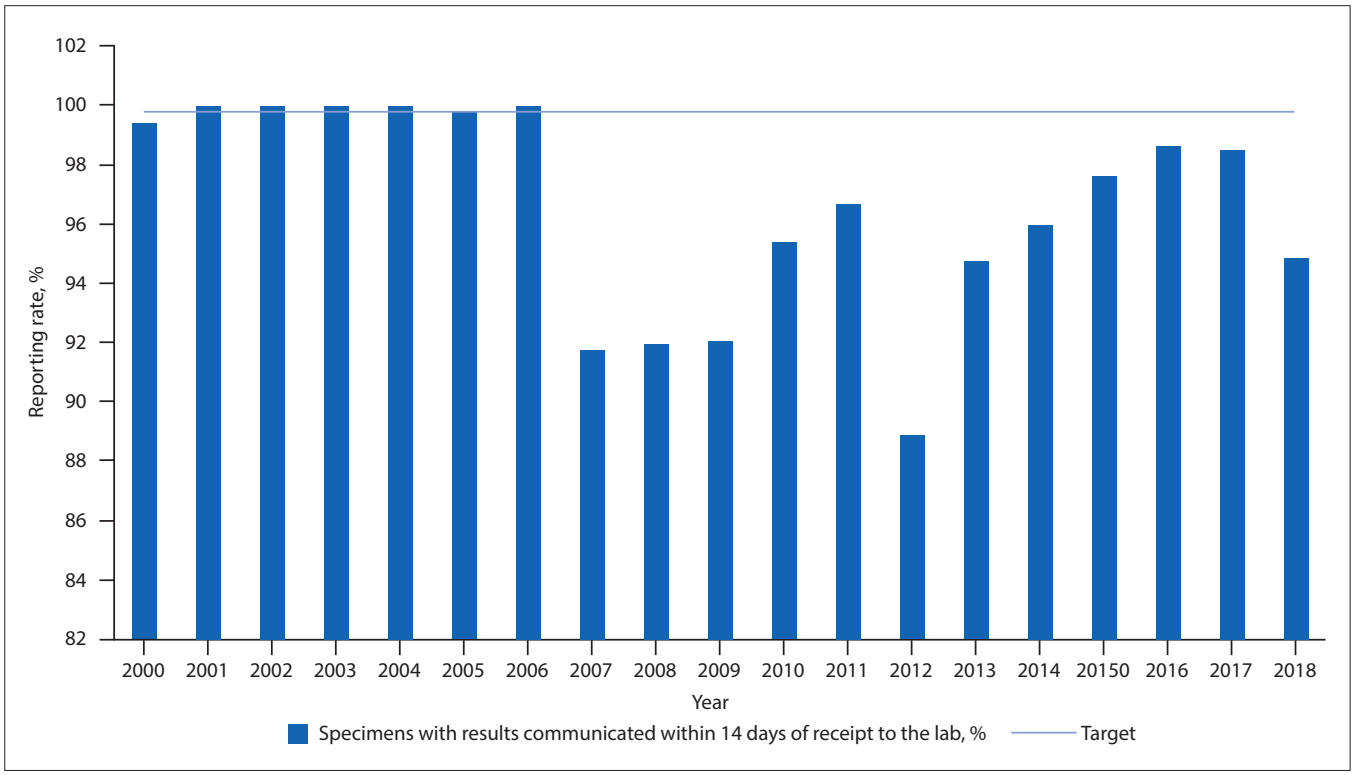

Fig. 4. Result reported within 14 days of specimen received in the laboratory, 2000 - 2018. The target is shown as a solid line.

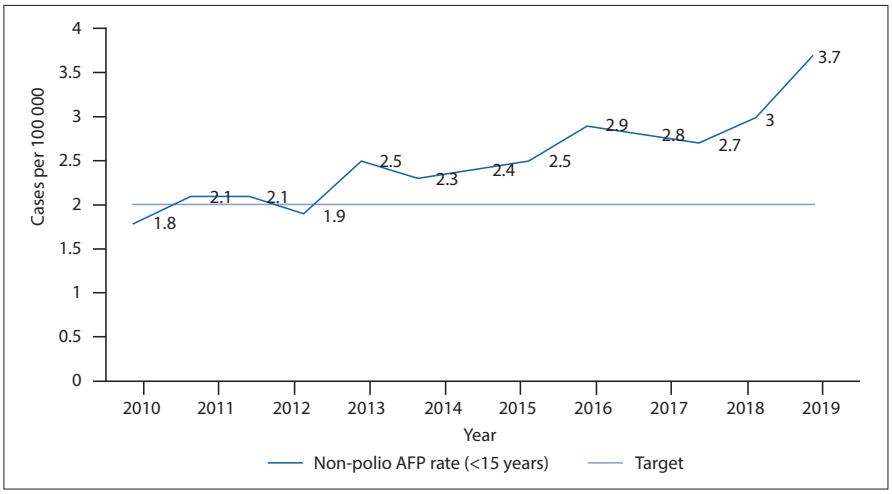

Fig. 5. Detected cased of non-polio acute flaccid paralysis in South Africa, 2007 - 2019. The target is shown as a solid line.

Fig. 6. Representatives of the African Region Certifications Committee during the verification visit following the reinstatement of South Africa's polio-free status.

optimally. For example, a campaign that focused on increasing demand for vaccination among under-5s was used as a platform to raise awareness about polio eradication.[19]

3. Commitment by political leaders and high-level advocacy contributed to resource mobilisation, motivating and inspiring implementation at all levels.
4. Strengthening health systems through quality improvement approaches was helpful in developing tailored district and provincial activities.
5. Collaboration by the national Department of Health, WHO, UNICEF, National Institute for Communicable Diseases, polio committees and provincial structures in providing technical support and mobilising resources to address the gaps was key in achieving the goal.
6. Through the collaborative efforts of the Department of Health and its partners demand for improved immunisation coverage increased and understanding of measles and AFP case definition was improved at the community level. This was done through aligning with campaigns that target national, regional and community radio stations, as well as harnessing the MomConnect and NurseConnect initiatives to improve awareness.[19,20]
7. The role of new technology and innovations such as the open data kit roll-out improved documentation of active-case search and surveillance supervision visits.[16]
8. Filling critical vacant positions (e.g. data manager and EPI specialist) at national level ensured close monitoring of the polio indicators and individualised support to address the gaps. In addition, ministerial communications on ensuring that targets for polio indicators were met spurred implementers to use data for planning and improved accountability.

Discussion

The high migration rates across SA's porous borders puts the country at risk of importing or exporting polioviruses.[21] Therefore, it is critical that a good surveillance system and high immunisation coverage should be in place to detect and prevent. In December 2017, the ARCC rescinded the country's polio-free status owing to observed gaps in the national polio surveillance system.[14] Maintaining immunisation coverage and a sensitive surveillance system after being certified polio free is critical to retain the status.[5] This paper describes the SA experience of losing and regaining a polio-free status.

Firstly, the ARCC had two advocacy visits to the country and engaged with authoritative role players across all levels of implementation.[14] These advocacy visits were key in rekindling the national political commitment to prioritise and mobilise resources to strengthen polio surveillance structures. For example, ministerial communications demanding prioritisation of reaching the target indicators and allocating resources to fill important vacancies followed these advocacy visits.

Furthermore, identifying existing gaps and possible solutions during the quality improvement processes assisted in addressing the health systems gaps.[22] Strengthening health systems in provinces, districts and at a facility level helped to promote the use of data to identify and address gaps. Such support needs a continued, individualised approach, as seen in the performance of districts and provinces on key indicators. Therefore, continuous quality improvement would be key in sustaining the strengthened health systems gains.[23]

In addition, collaboration between partners and the uptake of innovative technology (e.g. the open data kit) have shown to be instrumental, as these measures improved the supervision rate for polio surveillance.[16] The roll-out and expansion of environmental surveillance were critical in complementing the existing AFP surveillance system.[18] In this case, both the use of the

open data kit and implementing environmental surveillance were supported by the national WHO office.

Conclusion

This paper highlights that without effective leadership, commitment and monitoring, it is very easy for the long-term national poliovirus surveillance programme to break down, putting the African region at risk. Therefore, continued national support in maintaining and sustaining the national health programmes is critical to prevent the initiative from being neglected and risk the country losing its polio-free status.[14]

Declaration. None.

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Paediatric gastrointestinal endoscopy: Experience in Red Cross War Memorial Children's Hospital, Cape Town, South Africa

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Background. Endoscopy is an important diagnostic and therapeutic mode of management in children with gastrointestinal disorders.
Objective. To determine the indications, endoscopic yields and impact of the service on the ongoing health and complications among children who underwent gastrointestinal endoscopy at Red Cross War Memorial Children's Hospital, Cape Town.
Methods. A 10-year (2007 - 2016) retrospective study of children <18 years old who underwent gastrointestinal endoscopy was undertaken using relevant patients' variables obtained from their hospital medical records. Data were analysed using Stata 13.1 (p<0.05).
Results. A total of 402 children underwent a total of 695 gastrointestinal endoscopic procedures: 592 (85.2%) were gastroscopies, 78 (11.2%) combined gastroscopies with colonoscopies and 25 (3.6%) colonoscopy-only procedures, respectively. The main diagnostic indications for gastroscopy, gastroscopy combined with colonoscopy and colonoscopy-only were chronic abdominal pain (n=49; 12.2%), suspected inflammatory bowel disease (n=30; 7.5%) and rectal bleeding (n=13; 52.0%) respectively. The most common therapeutic indication for gastroscopy was change of a percutaneous endoscopic gastrostomy (n=143; 35.6%) while for colonoscopy 6 (5.8%) had polypectomy. Abnormal histopathological results were made from both macroscopically normal- and abnormal-looking tissues, though with no statistically significant relationship.
Conclusion. Endoscopy offers diagnostic and therapeutic options in children. Positive histological findings were obtained in some cases where gastrointestinal mucosae appeared normal. There is need to obtain biopsies from both macroscopically normal- and abnormal-looking gastrointestinal mucosae as positive histological findings could be made from them and hence improve diagnostic yield.

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Endoscopy has evolved to become an invaluable tool in the diagnosis and therapy of a variety of gastrointestinal disorders[1,2] in children, owing to the technological advancements in endoscopy designs and its devices.[3,4]

Improvements in sedation, anaesthesia[4] equipment and monitoring of vital signs of patients[5] during endoscopic procedures have added to the increased and safe use of gastrointestinal endoscopy in children, particularly younger infants and neonates.[5-7]

Indications for gastrointestinal endoscopy are diverse and fundamental to the assessment, treatment and follow-up/surveillance of children with gastrointestinal disorders, providing high diagnostic and therapeutic yields.[8]

Histopathological examination of tissue biopsies obtained from both macroscopically normal- and abnormal-looking tissues at endoscopy has improved the diagnosis of some gastrointestinal diseases.[9]

The sensitivity of endoscopic examinations varies with the age of the child and indication for the oesophagogastroduodenoscopy (OGD) and colonoscopy procedures, respectively.[10,11] Generally, gastrointestinal endoscopy has stood out as an accurate and informative method of assessing upper and lower gastrointestinal disorders, and endoscopic procedures should therefore be performed only in clinical conditions in which they have shown superiority over other diagnostic methods, including gastrointestinal contrast studies, X-rays and ultrasonography, among others.[8,12]

Various expert groups and organisations including the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) as well as the European Society of Gastrointestinal Endoscopy (ESGE),[12,13] and experts in the field,[14] have assessed the different guidelines for the use of gastrointestinal endoscopy in children, and recommended that there should be clear indications for undertaking an endoscopic procedure to ensure that its findings impact on patient management.

There is a paucity of data on paediatric gastrointestinal endoscopy in sub-Saharan Africa, including South Africa (SA), with most studies jointly reported by paediatricians in conjunction with adult gastroenterologists.[15-17]

The current study is a 10-year clinical audit of the paediatric gastrointestinal endoscopies conducted by paediatric gastroenterologists and trainee fellows under supervision in a paediatric specialist tertiary centre, Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, SA.

Although several published guidelines exist on paediatric gastrointestinal endoscopy from developed countries, it is envisaged that considering the long-standing experience of continuous gastrointestinal endoscopy programme in the centre, its findings will be more adaptable to most resource-poor/limited settings, particularly in sub-Saharan Africa.

Such findings will help paediatric gastroenterologist(s) and by extension paediatricians, with interests in endoscopy services to expand and improve on the quality as well as outcome of their gastrointestinal endoscopy services.

The objectives of the study were to assess the presenting symptoms, indications, histological yields, impact on management and complications among children and adolescents who underwent medical gastrointestinal endoscopy at RCWMCH, Cape Town.

Method

Study setting

This study was conducted at RCWMCH, which is a tertiary paediatric hospital affiliated to the University of Cape Town, SA.

All gastrointestinal endoscopies in children in the hospital were done following standard protocols by either consultant paediatric gastroenterologist(s) or trainee paediatric gastroenterology fellows under supervision. All gastrointestinal endoscopies in the unit were done under general anaesthesia administered by anaesthetists. RCWMCH only treats patients up to 13 years of age unless they have a chronic illness, and then they are followed up until 18 years of age.

At RCWMCH, cases of foreign body or caustic ingestions, oesophageal dilatations and laparoscopic percutaneous endoscopic gastrostomy (PEG) insertion were undertaken by the paediatric surgical team on separate endoscopy lists, and did not form part of this review.

Study design

This was a retrospective cross-sectional descriptive study undertaken among children and adolescents who underwent upper and lower gastrointestinal endoscopies performed by paediatric medical gastroenterologists from 1 January 2007 to 31 December 2016. This study did not include procedures performed by the paediatric surgeons in the centre.

Ethical approval

Study ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (ref. no. 089/2017), while written permission was obtained from the RCWMCH research committee and management prior to the commencement of the study.

Inclusion criteria

All children who had an OGD and/or colonoscopy with complete medical records were included in the study.

Exclusion criteria

Patients who underwent gastrointestinal endoscopy but with incomplete medical records during the period under review were excluded.

Procedure

All gastrointestinal endoscopies were performed under general anaesthesia. At gastroscopy (OGD), multiple tissue biopsies were taken from the oesophagus, stomach and duodenum, even if the tissue macroscopically looked normal.

All colonoscopy biopsies were taken from multiple sites in the colon. The patients were usually admitted a day before the procedure, during which time they underwent standard bowel preparation using polyethylene glycol (GoLytely; PEG) at a dose of 80 mL/kg body weight, usually starting from ~13h00 on the day before the procedure, and given only a soft lunch and no supper. The PEG is usually given orally, and in infants and younger children who cannot drink effectively, it is given via a nasogastric tube in graded doses until the bowel is clear.

Study datasheet

Information retrieved for each patient included sociodemographic characteristics, initial presenting symptoms, type of gastrointestinal endoscopy performed (gastroscopy, combined gastroscopy with colonoscopy or colonoscopy only) with specific indication(s), macroscopic findings on endoscopy, complication(s) following endoscopy, histological diagnosis and impact on management following the endoscopic procedure.

The data were collected from the hospital's medical records as well as the paediatric gastroenterology unit and endoscopy and histopathology databases, and captured on a study datasheet.

Diagnostic characteristics

Diagnostic yield of endoscopy in the current study was classified as either positive (presence of any macroscopic endoscopy and/or histological abnormality found, excluding mild inflammation on histology) or negative (no or minor abnormality/normal histology) effecting a positive contribution.[18,19]

Mild inflammation was not regarded as a positive histological outcome as the clinical significance of isolated mild histological findings is inconclusive.[18,19]

Endoscopy diagnostic yield was calculated for initial examination involving diagnostic indications for upper and lower endoscopy, respectively.

Socioeconomic class determination

Patients were classified as low (H0 or H1), middle (H2) or high (H3) socioeconomic class (SEC) according to their gross income per annum for the purposes of service fee determination, according to the uniform fee schedule regulations for healthcare services rendered by the Western Cape Province, Department of Health, SA, 2017.[20]

Data analysis

Data analysis was done using Stata 13.1 (Stata Corp, USA). Categorical variables were presented as frequency tables and charts, while numerical variables were presented as descriptive measures, expressed as median and range.

The association between categorical variables was assessed using the Pearson χ^2 test or Student's *t*-test where appropriate. A *p*-value <0.05 was considered statistically significant.

Results

Characteristics of study participants

A total of 402 patients with complete medical records were studied. There were 220 (54.7%) girls, with a female-to-male ratio of 1:0.8. Their median age was 5.5 (range: 0.1 - 18) years, 394 (98.0%) were <13 years old and of normal weight (*n*=276; 68.6%), and most were of low SEC (*n*=307; 76.4%) (Table 1).

Endoscopic procedures

Of the total 695 gastrointestinal endoscopic procedures, 592 (85.2%) were gastroscopies, 78 (11.2 %) gastroscopies combined with colonoscopies and 25 (3.6%) colonoscopy only (Table 1). The median numbers of gastroscopies and colonoscopies performed per patient were 1 (range 1 - 12) and 2 (1 - 4), respectively.

Presenting symptoms

The presenting symptoms for gastroscopy, combined gastroscopy

with colonoscopy and colonoscopy only were as shown in Figs 1, 2 and 3, respectively.

The most common presenting symptoms in children undergoing gastroscopy (as shown in Fig. 1) were patients evaluated for PEG insertion for feeding (therapeutic gastroscopy) due to feeding difficulty/inco-ordinate swallowing in children with cerebral palsy (*n*=214; 53.2%), and poor weight gain/failure to thrive (*n*=145; 36.1%), followed closely by those with chronic abdominal pain (*n*=103; 25.6%) and upper gastrointestinal bleeding (*n*=81; 20.1%). In patients who had combined gastroscopy with colonoscopy, the most common presenting symptoms were chronic abdominal pain (*n*=37; 47.5%), chronic bloody loose stools (*n*=35; 44.9%) in older children and chronic diarrhoea (*n*=30; 38.5%), as shown in Fig. 2.

In patients who underwent colonoscopy only, the most common presenting symptoms were rectal bleeding (*n*=13; 52.0%) and chronic bloody loose stools (*n*=9; 36.0 %) (Fig. 3).

Table 1. Sociodemographic and endoscopic characteristics of study subjects (*N*=402)

Characteristic	*n* (%)*
Age (years), median (range)	5.5 (0.1 - 18.0)
Sex	
Male	182 (45.3)
Female	220 (54.7)
Socioeconomic class	
Low	307 (76.4)
Middle	57 (14.2)
High	38 (9.5)
Weight for age z-score	
–1 - < 0 (normal)	276 (68.6)
–2 - <–1 (marginal underweight)	23 (5.7)
–3 - <–2 (moderately underweight)	42 (10.4)
<–3 (severe underweight)	61 (15.2)
Endoscopy performed	
Total gastroscopy and colonoscopy (patient encounters)	695 (100.0)
Gastroscopy only	592 (85.2)
Combined gastroscopy and colonoscopy	78 (11.2)
Colonoscopy only	25 (3.6)

*Unless otherwise indicated.

Indications for endoscopy

Oesophagogastroduodenoscopy (OGD)

Among 592 gastroscopies performed, 179 (30.2%) were diagnostic, 287 (48.5%) therapeutic and 126 (21.3%) for follow-up/surveillance.

The main diagnostic indications for gastroscopy were chronic abdominal pain (*n*=49; 8.3%), upper gastrointestinal bleeding/portal hypertension with varices (*n*=43; 7.3%) and gastritis/gastro-oesophageal reflux (*n*=30; 5.1%), while the therapeutic indications for gastroscopy included insertion of PEG tube (*n*=87; 14.7%), change of PEG to gastrostomy tubes (*n*=143; 24.6%), variceal sclerotherapy of oesophageal varices (*n*=29; 4.9%) and variceal band ligation (*n*=28; 4.7%).

The follow-up/surveillance indications for OGD were mainly for previous upper gastrointestinal bleeding secondary to oesophageal varices, 204 (50.7%) (Table 2).

Combined OGD with colonoscopy

Of the 78 combined gastroscopy and colonoscopy procedures, the majority (*n*=68; 87.2%) were for diagnostic indications, which included probable inflammatory bowel disease (IBD; *n*=30; 38.5%), chronic diarrhoea (*n*=12; 15.4%), suspected intestinal tuberculosis (TB; *n*=10; 12.8%), chronic abdominal pain (*n*=8; 10.3%), chronic iron deficiency anaemia of unknown aetiology (*n*=3; 3.8%) and IBD screening in those with autoimmune hepatitis (*n*=3; 3.8%). The follow-up/surveillance indications were for inflammatory bowel disease (*n*=10; 12.8%) (Table 2).

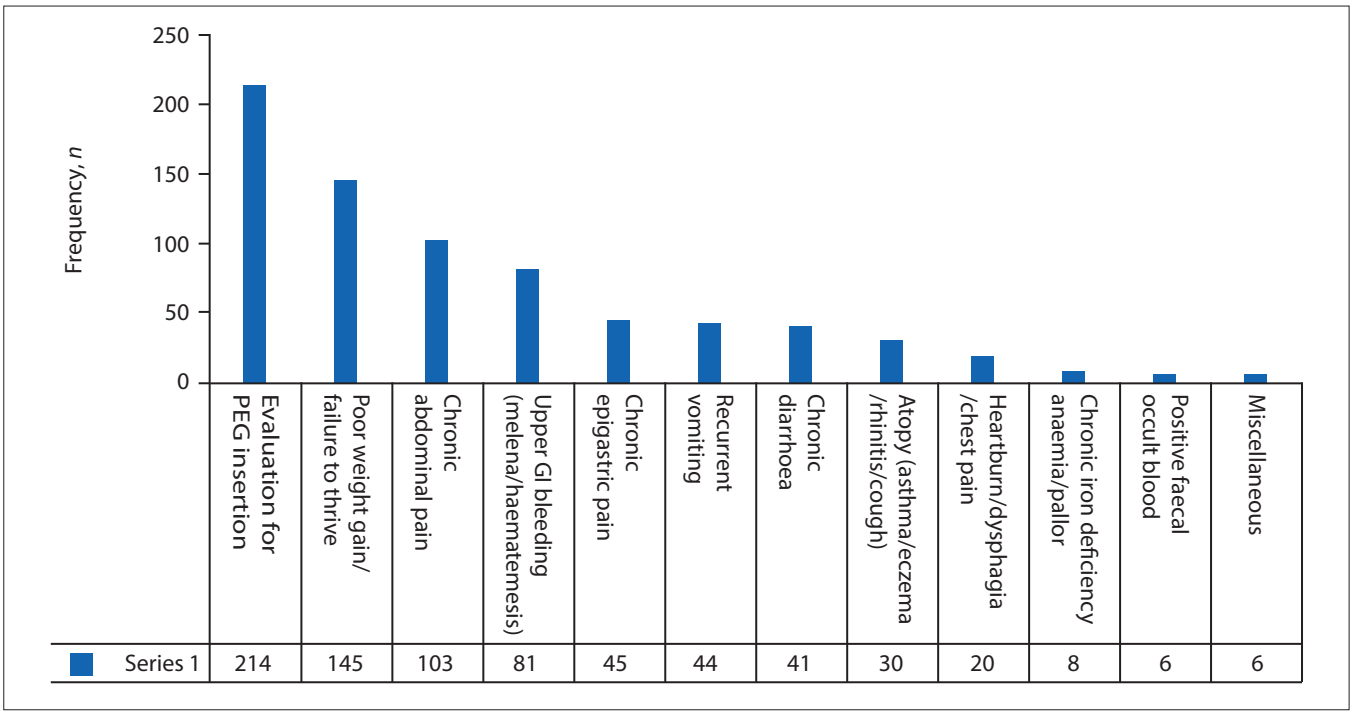

Fig. 1. Presenting symptoms of participants who underwent endoscopy: gastroscopy only (n=592). (PEG = percutaneous endoscopic gastrostomy; GI = gastrointestinal.)

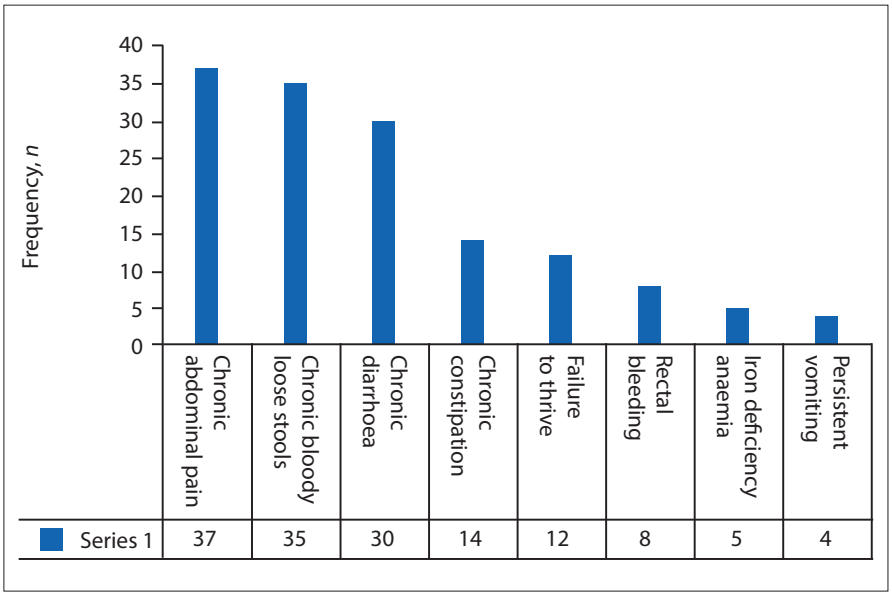

Fig. 2. Presenting symptoms of participants who underwent endoscopy: combined gastroscopy and colonoscopy (n=78).

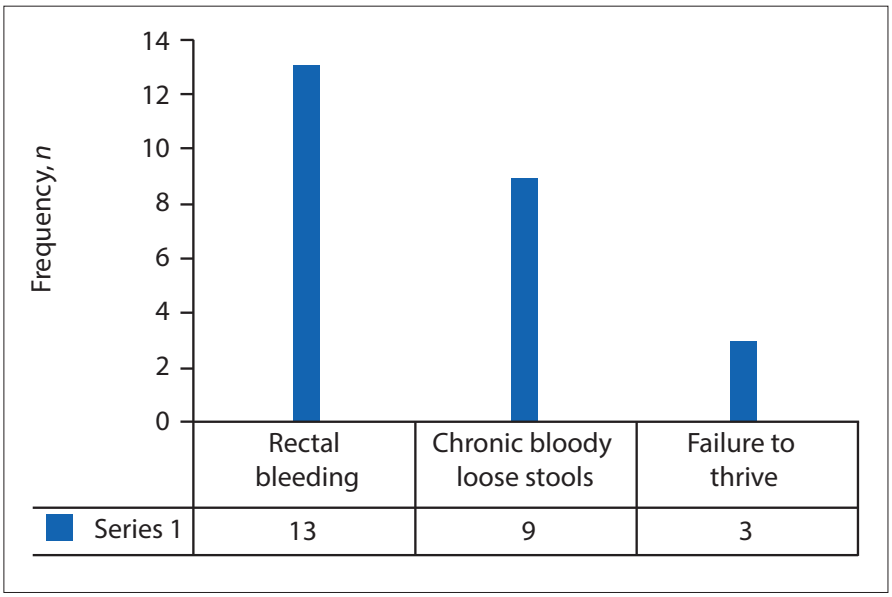

Fig 3. Presenting symptoms of participants who underwent endoscopy: colonoscopy only (n=*25).*

Colonoscopy

Of 25 (100%) colonoscopy-only procedures undertaken, 13 (52%), 6 (24%) and 6 (24%) were for diagnostic, therapeutic and follow-up/surveillance indications, respectively.

Six (24%) therapeutic colonoscopy procedures were performed for polypectomy, while in another 6 (24%) cases, colonoscopies were undertaken for IBD follow-up/surveillance cases (Table 2).

Terminal ileum intubation and caecal examination rate

Terminal ileal intubation was attempted in diagnostic colonoscopy procedures undertaken as combined gastroscopy and colonoscopy or colonoscopy-only procedures as follows: 68 (87.2%) diagnostic combined gastroscopy with colonoscopy, 13 (52%) diagnostic and 6 (24.0%) follow-up/surveillance colonoscopy-only procedures, totalling 87 patient procedures.

Of the 87 diagnostic colonoscopies performed, complete terminal ileum intubation with caecal examination was achieved in 85 (97.7%) cases. All cases of suspected IBD and/or small-bowel disease also had magnetic resonance enterography in addition to endoscopy.

Diagnostic yields

Gastroscopy

A total of 179 gastroscopies were for diagnostic purposes, of which 43 were for upper gastrointestinal bleeding, with the majority being oesophageal varices diagnosed macroscopically during endoscopy. Histology was only done in 5 of these cases. In all other cases, biopsies were taken and the histological results showed normal findings in 107 (18.1%), chronic gastritis in 33 (5.6%) and eosinophilic oesophagitis (EoE) in 7 (1.5%) (Fig. 4).

Colonoscopy

A total of 103 colonoscopies were undertaken, comprising 78 cases of combined gastroscopy with colonoscopy (68 being for diagnostic and 10 cases for follow-up surveillance) and 25 colonoscopies only (13 diagnostic, 6 therapeutic and 6 surveillance).

Initial diagnoses were considered. Of the 81 diagnostic colonoscopies (68 diagnostic combined gastroscopy with colonoscopy, and 13 colonoscopy only), multiple tissue biopsies were taken for histology (*n*=25; 24.3%) and had normal histological findings, and IBD was found in 19 (18.4%) cases, of which 10 (9.7%) were Crohn's disease and 9 (8.7%) ulcerative colitis.

Abnormal histopathological results were seen in biopsies taken from macroscopically normal-looking gastrointestinal mucosa (*n*=15), for diagnostic gastroscopies (*n*=15/179; 8.4%), combined gastroscopy and colonoscopy (*n*=6/68; 8.8%) and colonoscopies only (*n*=2; 15.4%) of the diagnostic procedures.

However, there was no statistically significant relationship between positive histological findings from tissue biopsies taken from macroscopically normal and abnormal gastrointestinal mucosae during gastroscopy (x^2=6.419; *p*=0.526) and combined gastroscopies and colonoscopies (x^2=5.142; *p*=0.275), respectively (Table 3).

Eight (9.9%) out of 10 probable cases of intestinal TB were diagnosed on histology. Chest radiographs showed evidence of healed TB (fibrosis and/or calcification) in 6 patients, and active pulmonary TB (presence of acid-fast bacilli in induced sputum) in 2 patients. Ulcerated areas and nodular friable mucosa were the most common lesions on colonoscopy. *Mycobacterium tuberculosis* was only cultured from three of the biopsies.

Histology

The majority (*n*=107; 18.1%) of tissue biopsies taken during gastroscopies had normal histological findings, although 33 (5.6%) showed chronic gastritis, 9 (1.5%) EoE and 7 (1.2%) *Helicobacter pylori*-associated gastritis (Fig. 4).

Normal histological findings were found in 25 (30.9%) diagnostic colonoscopies. IBD

Table 2. Indications for gastrointestinal endoscopy among study subjects

Characteristic	*n* (%)
Gastroscopy only (*n*=592 patient encounters)*	
Diagnostic (*n*=179)	
Chronic abdominal pain	49 (8.3)
Upper gastrointestinal bleeding/portal hypertension	43 (7.3)
Gastritis/gastro-oesophageal reflux	30 (5.1)
Probable eosinophilic oesophagitis	17 (2.9)
Chronic diarrhoea	17 (2.9)
Suspected coeliac disease	9 (1.5)
Miscellaneous†	6 (1.0)
Recurrent aspiration	5 (0.8)
Cyclical vomiting	3 (0.5)
Therapeutic (*n*=287)	
Change of PEG	143 (24.6)
Insertion of PEG	87 (14.7)
Sclerotherapy for varices with PHT	29 (4.9)
Band ligation for varices with PHT	28 (4.7)
Follow-up/surveillance (*n*=126)	
Upper gastrointestinal varices	126 (21.3)
Combined gastroscopy and colonoscopy (*n*=78)	
Diagnostic (*n*=68)	
Probable inflammatory bowel disease (IBD)	30 (38.5)
Chronic diarrhoea	12 (15.4)
Intestinal tuberculosis	10 (12.8)
Chronic abdominal pain	8 (10.3)
Chronic iron deficiency anaemia	3 (3.8)
IBD with autoimmune hepatitis	3 (3.8)
Probable protein-losing enteropathy	2 (2.6)
Follow-up/surveillance (*n*=10)	
Inflammatory bowel disease	10 (12.8)
Colonoscopy only (*n*=25)	
Diagnostic (*n*=13)	
Lower gastrointestinal bleeding (rectal bleeding)	13 (52.0)
Therapeutic (*n*=6)	
Polypectomy	6 (24.0)
Follow-up/surveillance (*n*= 6)	6 (24.0)

PEG = percutaneous endoscopic gastrostomy; PHT = portal hypertension; IBD = inflammatory bowel disease.
*Multiple entries apply in the table (i.e. some patients had more than one endoscopic indication).
†Miscellaneous: recurrent sore throat (*n*=1), obesity (*n*=2), epistaxis (*n*=1), chronic non-steroidal anti-inflammatory drug use (*n*=1).

was diagnosed in 19 (23.5%) patients, made up of Crohn's disease (*n*=10; 12.3%) and ulcerative colitis (*n*=9; 11.1%), intestinal polyps in 9 (11.1%) and intestinal TB in 8 (9.9%) (Fig. 5).

Impact of gastrointestinal endoscopy on management

The various endoscopic procedures showed differing impacts on the management of cases in various ways. Out of 592 gastroscopies, 87 (14.7%) were done in patients with cerebral palsy or other neurological disorders with failure to thrive, and required PEG insertion for optimal feeding, while 57 (9.6%) had endoscopic treatment for oesophageal varices, which included sclerotherapy (*n*=29; 4.9%) and variceal band ligation (*n*=28; 4.7%). In addition, 8 (1.4%) and 2 (0.3%), respectively, had addition of new medication(s) and therapy for eradication of *H. pylori* following histological diagnoses. The majority (*n*=295; 49.8%) of cases had no significant findings on histology and did not require further treatment, and ongoing treatments were discontinued.

In 78 patients who underwent combined gastroscopy and colonoscopy procedures, 35 (44.9%) had addition of new medication(s) to their treatment, 5 (6.4%) were prescribed nutritional therapy using exclusive enteral nutrition for Crohn's disease/minimal fat diet, 2 (2.6%) change of medication(s) for differing gastrointestinal conditions, and 36 (46.1%) had no change or further treatment post colonoscopy based on review of histology and other results.

In 25 colonoscopies, 8 cases (32%) had change of medication(s) for different gastrointestinal conditions, and 5 (20%) addition of new medications. Six cases (24%) had polypectomy, and another 6 (24%) no change or no further treatment post colonoscopy, with review of histology and other results.

PEG insertion/change

Of the total of 230 PEG procedures performed during the period under review, 87 (37.8%) were PEG insertions, while 143 (62.2%) had change of the initial PEG to gastrostomy tubes. The indications for PEG insertion were feeding difficulty/inco-ordinate swallowing (mainly in children with neurological deficits, particularly cerebral palsy and traumatic brain injury) with failure to thrive/poor weight gain (*n*=85; 21.1%) and inco-ordinate swallowing at risk of poor medication (antiretroviral) adherence, 2 (0.5%) in patients with AIDS. PEGs were changed to a gastrostomy tube after a mean period of 3.7 (range 3 - 12) months. In 2 (1.4%) patients aged 7 and 10 years, respectively, initial PEG tubes were later changed to a MIC-KEY type of gastrostomy tube on request of the attending caregivers. There was significant increase in patients' weight upon their feeding using gastrostomy tubes post insertion. Among the 87 (37.8%) participants who had PEG insertion, the pre-PEG insertion mean weight was 11.4 kg, and increased to 13.5 kg at the time of change of PEG to gastrostomy tube ($p<0.001$).

Safety/complications

Endoscopic procedures undertaken among study participants were safe. Of a total of 695 endoscopies (592 gastroscopies, 78 combined gastroscopies with colonoscopies and 25 colonoscopies alone), complications occurred in 7 (1.0%). Most of these complications were related to the cardiovascular/respiratory system and anaesthetic.

Complications occurred post gastroscopy: pneumo-peritoneum in 1 patient (0.2%) post PEG insertion, desaturation in 1 (0.2%) and 1 (0.2%) failed extubation.

Among those who underwent combined gastroscopy with colonoscopy procedures, out of 78 procedures, there were 3 complications: 1 child (1.3%) had stridulous breathing on extubation and another bradycardia/hypotension, while in participants who had colonoscopy only (*n*=25), 1 case (4%) of bradycardia/hypotension was observed.

Discussion

Recent advances in endoscopy designs and devices have made endoscopy an invaluable tool in diagnosis, therapy and follow-up/surveillance of most gastrointestinal disorders in paediatric and child health practices.[2,13] Literature is scarce on paediatric gastrointestinal endoscopy in sub-Saharan Africa. It is hoped that experience gained in the present study will guide practice in many centres in the region and other parts of the developing world in setting up a paediatric gastrointestinal endoscopic service.

The present study is a comprehensive clinical audit of paediatric gastrointestinal endoscopy service undertaken by paediatric

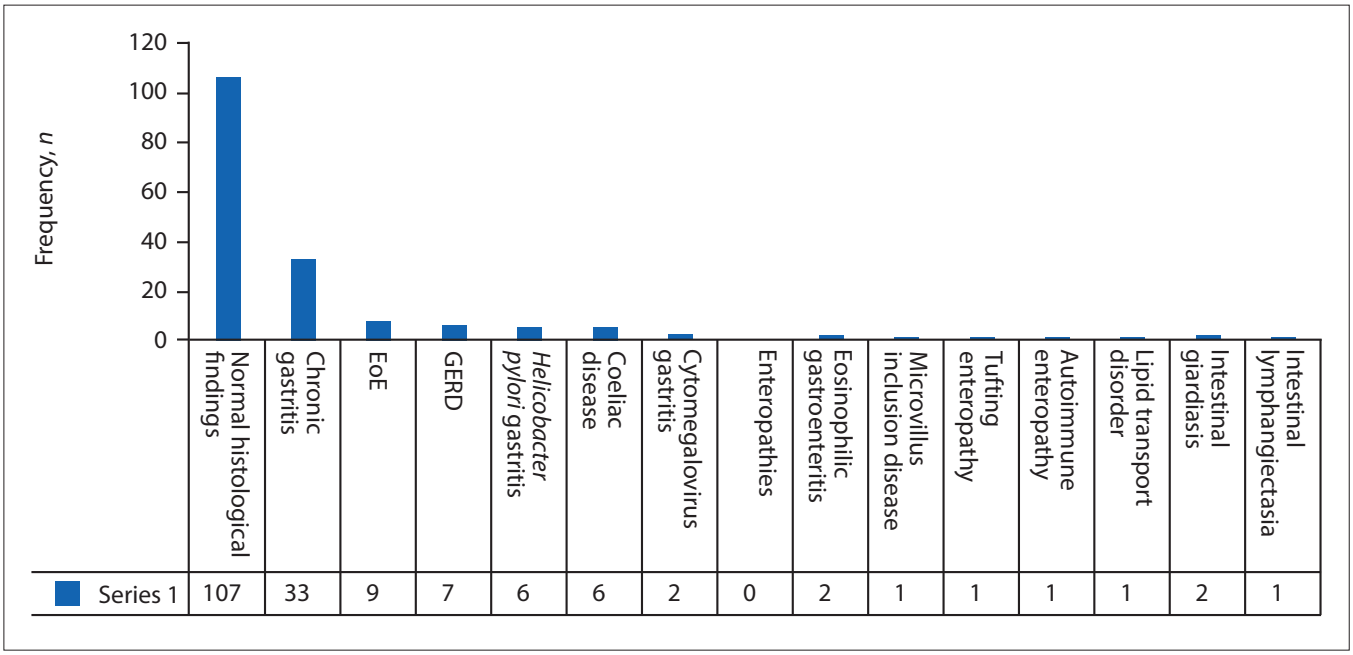

Fig. 4. Histological yields among study participants who underwent diagnostic gastroscopy (n=*179). (EoE = eosinophilic oesophagitis; GERD = gastro-oesophageal reflux disease.)*

Table 3. Relationship between histological yield in normal and abnormal macroscopy in children undergoing diagnostic endoscopy

Endoscopic modality	Indications for endoscopy	Positive histology from abnormal macroscopy, *n/N* (%)	Positive histology from normal macroscopic tissues, *n/N* (%)	*p*-value (Fisher's exact)
Gastroscopy				0.526
	Chronic abdominal pain	31/49 (63.3)	5/49 (10.2)	
	Upper GI bleeding*	3/43 (7.0)	0/43 (0.0)	
	Gastritis/GERD	15/30 (50.0)	2/30 (6.7)	
	EoE	6/17 (35.3)	3/17 (17.6)	
	Chronic diarrhoea	9/17 (52.9)	1/17 (5.9)	
	Coeliac disease	5/9 (55.6)	1/9 (11.1)	
	Recurrent aspiration	2/5 (40.0)	1/5 (20.0)	
	Cyclical vomiting	1/3 (33.3)	1/3 (33.3)	
	Miscellaneous†	3/6 (50.0)	1 /6 (16.7)	
	Total	75/179 (41.9)	15/179 (8.4)	
Gastroscopy and colonoscopy				
	Probable IBD	14/30 (23.3)	2/30 (6.7)	0.275
	Abdominal TB	7/10 (70.0)	1/10 (10.0)	
	Chronic diarrhoea	8/13 (61.5)	0/13 (0.0)	
	Chronic abdominal pain	3/8 (37.5)	2/8 (25.0)	
	Chronic iron deficiency anaemia	2/3 (66.7)	1/3 (33.3)	
	Autoimmune hepatitis with IBD	3/3 (100)	0/3 (0)	
	Total	37/68 (54.4)	6/68 (8.8)	
Diagnostic colonoscopy only (*n*=13)				
	Unexplained lower GI bleeding	7/13 (53.8)	2/13 (15.4)	-
	Total	7/13 (53.8)	2/13 (15.4)	

GI = gastrointestinal; GERD = gastro-osoephageal reflux disease; EoE = eosinophilic oesophagitis; IBD = inflammatory bowel disease; TB = tuberculosis.
*Histology was done only in 3 cases of upper GI bleeding/portal hypertension (gastroscopy) as most were varices and diagnoses made macroscopically with histology of tissue biopsies.
†Miscellaneous: recurrent sore throat (*n*=1); cyclical vomiting (*n*=2); non-steroidal anti-inflammatory drugs/steroid use (*n*=1).

gastroenterologists and trainees in a paediatric specialist centre in Cape Town, SA.

Most patients in the current study were young, with only 2% (8) of them aged >13 years. The hospital's cut-off for seeing new patients is age 13 years, and special permission must be sought to treat or continue to care for children >13 years old in the centre.

Most gastrointestinal disorders present with nonspecific signs and symptoms, making definitive diagnoses difficult without endoscopy

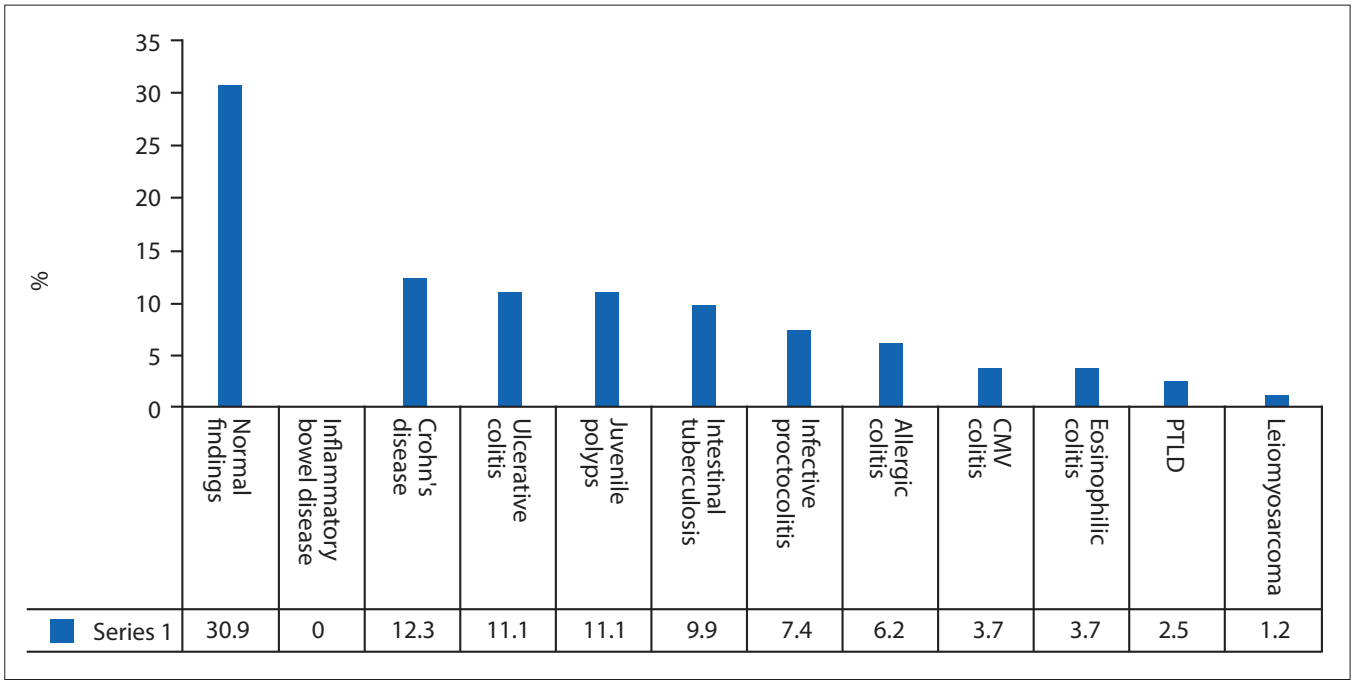

Fig. 5. Histological yields among study participants who underwent diagnostic colonoscopy (including combined gastroscopy and colonoscopy (n=*68) and colonoscopy alone* (n=*13)* (N=*81). (CMV = cytomegalovirus; PTLD = post-transplant lymphoproliferative disease.)*

in some cases.[8,13] However, there is a need to apply local experience and standard expert societal guidelines in centres running paediatric endoscopic services so as to improve diagnostic yields, which will ultimately impact on patient management. Abdominal pain was the most common indication for endoscopy among participants in the present study, which has been corroborated by authors in most similar studies.[16,19] Also, evaluation for PEG insertion in children with feeding difficulties/inco-ordinate swallowing and poor weight gain/failure to thrive were the prevalent therapeutic indications for gastroscopy. PEG tubes were mainly inserted for improved feeding in cases of inco-ordinate swallowing due to neurological disorders. Sclerotherapy or band ligation for oesophageal varices were the second-most common indications for therapeutic gastroscopy in the current study. Rectal bleeding and chronic bloody loose stools were the two leading indications for colonoscopy in the present study, and this has also been corroborated by other studies.[21,22] The experience in the current study also corroborates the recommendations by key expert societal guidelines on common indications for performing endoscopy in children,[13] based on the presenting symptoms, and underscores the need to adhere to them for utmost endoscopic impacts and outcomes. Combined gastroscopy and colonoscopy procedures are the benchmark for the diagnosis and follow-up of some paediatric gastrointestinal disorders, particularly IBD (Crohn's disease, ulcerative colitis or indeterminate IBD), polyposis and eosinophilic colitis, among others,[23,24] as found in the present study.

Endoscopy is an important diagnostic and therapeutic tool in children. Various gastrointestinal disorders have been diagnosed with the aid of endoscopy, as in the current study. Some diagnoses were made macroscopically during endoscopy, e.g. oesophageal and gastric varices, EoE with concentric ring formation/trachealisation and longitudinal linear furrows and patches of small, white papules on the oesophageal surface (confirmed on histology),[25] while others were diagnosed from histopathology on biopsy specimens taken during endoscopy. Some therapeutic endoscopy procedures were employed, including sclerotherapy (in the younger infants/toddlers) and variceal band ligation (in older children), in managing cases of upper gastrointestinal bleeding from oesophageal varices and polypectomy for juvenile polyps.

In addition, follow-up scopes were done in cases of IBD to assess disease remission and relapses. Follow-up surveillance was done in cases of multiple juvenile polyposis for monitoring of development of colorectal carcinoma, as there is a 15% incidence of such malignancy in patients <35 years of age.[22,23]

Overall endoscopic yield for the various modalities of upper and lower endoscopy in the present study was high. The high endoscopic yield observed may be due to the appropriate selection of cases with correct indications for endoscopy using standard societal guidelines,[26] pre-procedure preparations including standard bowel preparations, as well as obtaining of biopsies at the time of endoscopy from both macroscopically normal- and abnormal-looking gastrointestinal mucosa. High diagnostic yields have equally been reported for OGD and colonoscopy in similar studies.[18,19,27,28]

Using standard societal guidelines, including the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), the correct indications for endoscopy will lead to a high impact rate on management of children with various gastrointestinal symptoms/disorders. Significant impacts on patient management were seen in patients with PEG insertions for feeding difficulties.

Improved oral intake allowed these children to meet their recommended dietary allowances, with attendant improved growth as evidenced by an increase in median weight-for-age *z*-scores (–2 - 0). Similar findings have been reported in other studies.[29,30] Children with portal hypertension and oesophageal varices causing upper gastrointestinal bleeding also benefited from either sclerotherapy or variceal band ligation, with good results depending on their age.[31]

In addition, a few of the patients in the current study with juvenile polyposis had snare polypectomy and subsequent follow-up/surveillance for possible development of associated malignancies.

There were cases in the present study where changes in treatment were made based on endoscopy. In cases of IBD with relapsing or

worsening disease activity based on either paediatric ulcerative colitis activity index scores[32] or Crohn's disease activity index scores,[33] escalation of medical therapy was required to improve the clinical outcome.

In a study by Thakkar *et al*.,[9] a 42% change in patients' management was made in their study, made up of a 20% change in management immediately following endoscopy and 18% post histology review, and 9% after both, respectively. In their study, management changes were mainly the addition of new medication(s) in children with IBD, particularly those with Crohn's disease, with improvement in their overall treatment outcomes, similar to the experience in the present study. Other benefits of endoscopies in our study participants included eradication of *H. pylori* in cases diagnosed on histology, and culture of the gastric antrum biopsies, as well as polypectomies of juvenile polyps, among others. Most of these gastrointestinal endoscopic impacts on management have been corroborated by researchers in similar studies.[25,29-31,34]

In paediatric endoscopies, it is advised to take biopsy specimens from both macroscopically normal- and abnormal-looking gastrointestinal mucosae for histology. This is because some gastrointestinal mucosa may appear macroscopically normal on endoscopy, but show pathology/abnormal histology. It has been reported that in ~20% of macroscopically normal upper gastrointestinal mucosa, biopsies reveal various pathological conditions on histology, thereby improving the rate of endoscopic yields in such cases.[35]

Limitations exist in gastroscopy and colonoscopy (diagnostic) in the evaluation of various gastrointestinal complaints in children, as some studies have reported no histological abnormalities in up to 60% of the sites biopsied, and in ~65%, no macroscopic abnormalities observed during endoscopy.[36] Negative histopathological findings on biopsies are useful in excluding pathology and thus reassuring and relieving anxiety in patients and their families,[28] as well as averting the need for further investigations, with resulting lowered economic costs in patient management. Considering the potential complications and costs of gastrointestinal endoscopy under general anaesthesia as in the current centre, appropriate clinical judgement and guidelines should be applied in selecting patients with the right indications for endoscopy.[37]

Terminal ileum intubation is an important indicator of complete colonoscopy. It is invaluable in the diagnosis of some specific gastrointestinal disorders, including IBD, intestinal TB and chronic diarrhoea, among others, that affect the gut.[38,39]

The terminal ileum intubation rate of 97.7% observed in the current study appears to be much higher than findings in similar studies,[38,39] and could have played a significant role in the overall outcome of the study. It is possible that the high level of bowel preparations in patients who underwent colonoscopy as well as the endoscopic skills of the experienced gastroenterologists resulted in the high rate of terminal ileum intubation. The histopathology of terminal ileal biopsies was essential in distinguishing gastrointestinal disorders, including distinguishing intestinal TB from Crohn's disease, in which the former occurs commonly in the ileo-caecal gut.

Most cases of intestinal TB (n= 8; 9.9%) seen in the present study had histological features of the disease. TB is endemic in SA and is treatable, with good outcomes using anti-tuberculous agents for 6 months.[40] Patients with Crohn's disease may have coexisting latent TB, which is important to exclude as IBD immunosuppressive treatment could result in reactivation of latent TB and further disseminated TB. Intestinal TB needs to be excluded in our setting before starting immunosuppressive treatment in IBD cases.

There was a low complication rate recorded in the present study, with no mortality attributable to the endoscopic procedures reported. RCWMCH has an experienced anaesthetic department, and all paediatric gastrointestinal endoscopies were performed under general anaesthesia. Though a few cases of anaesthetic-related minor complications were reported, no mortality was recorded compared with use of intravenous sedation for endoscopy.

The majority of the complications (n=5/7; 71.4%) reported in the current study were anaesthetic related, as has been observed by other studies.[30,42] It is plausible that the use of standard expert societal guidelines in selecting patients for endoscopy in the current study improved pre-endoscopic preparations of patients, and that performance of the procedures by a gastroenterologist and/or trainee fellows under general anaesthesia administered by a consultant anaesthetist accounted for the low complication rate observed.

Conclusion

Endoscopy offers diagnostic and therapeutic options in children. Positive histological reports were recorded in some cases where gastrointestinal mucosae appeared normal. There is a need to obtain biopsies from both abnormal-looking and macroscopically normal mucosa, as significant histology could be made from these, hence improving diagnostic yield.

One limitation of the present study is that the retrospective nature of a longitudinal study might have revealed long-term outcomes of some of the cases.

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Male partners' experiences of early pregnancy ultrasound scans in Soweto, South Africa: The Healthy Pregnancy, Healthy Baby randomised trial

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Background. Despite international evidence highlighting the benefits of male partners attending antenatal visits, including pregnancy ultrasound scans, it is unusual for South African (SA) men to attend such visits, and little is known about their experiences if they do.
Objectives. To explore the experiences and antenatal attachment among male partners who attend early pregnancy ultrasound examinations in Soweto, SA.
Methods. Pregnant women attending ultrasound examinations were invited to bring their partners with them. Both completed individual questionnaires, including the antenatal attachment scale. The results are based on a descriptive analysis of 102 mother-partner pairs.
Results. The mean age of partners was 35 years. Only 32% of men were living with their pregnant partner. Before the ultrasound scan, 64% of men reported feeling very anxious, while 54% also felt anxious after the procedure. The ultrasound examination had a positive effect on men and their thoughts regarding their developing baby, with 30% stating that they were ready or excited to be a father. Twenty-eight percent believed their relationship with the mother was stronger as a result of participating in antenatal care.
Conclusions. We found that prenatal ultrasound scans had a positive effect on male partners and their thoughts about the pregnancy, their forthcoming child and their relationship with and support for their partner. Health services in SA should accommodate partners/fathers and encourage them to attend antenatal care, including pregnancy ultrasound scans. Interventions are needed to encourage more men to be involved – from conception – potentially addressing individual, familial, societal and structural barriers to involvement of the father in long-term maternal and child care.

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Research and interventions for pregnancy, antenatal care, maternal and child health and education focus mainly on mothers and children. Although the literature on male involvement during pregnancy and their experiences of antenatal services such as ultrasound scans is increasing, these factors remain limited in low- and middle-income countries (LMICs).[1] Fathers or male partners can play an important role by providing practical, emotional and financial support to their expectant partners. They can promote maternal health and wellbeing by encouraging positive behaviours such as healthier eating and increased exercising that indirectly impact fetal development, pregnancy term and birthweight.[2] Male partners can also discourage harmful behaviours, such as smoking and drinking alcohol, and encourage women to attend antenatal healthcare early.[3] Evidence suggests that the inclusion of fathers or male partners in both pre- and perinatal programmes positively impacts a child's attachment security, their emotional regulation and cognitive development. At the same time, such interventions can also positively impact male wellbeing and their relationship with the mother and child.[4]

Attendance at antenatal health visits, e.g. ultrasound appointments, has been shown to have a wide range of benefits. Harpel and Barras,[5] who studied the effects of maternal ultrasound scans on others, including men, found that men struggled more than mothers to cope with a complication or loss of pregnancy after attending an ultrasound examination.[5] It is hypothesised that the visual image of their forthcoming child establishes the reality of the pregnancy, which can strengthen the bond between expectant father and unborn child.[6-8] Male attendance at ultrasound scans has also been associated with improved child outcomes at birth. One study, for example, found that male ultrasound attendance was associated with a 7 percentage point reduction in premature infant births.[9] When male partners are involved, including attending ultrasound scans with their expectant partners, they are more likely to provide extra care and support, while regulating the stress levels of their partners, which can avert premature delivery.[10]

Many pregnant women want their male partners to be involved throughout the pregnancy, labour, delivery and development of their child,[11] and health professionals encourage men to attend antenatal appointments, including ultrasound scans.[12,13] Despite this, and evidence showing the positive impact of father involvement, men face a range of barriers in low- and middle-income settings,[4,11,14] and the timing of health visits that conflict with work schedules,[15] coupled with inflexible clinic hours or under-resourced health services.[16] In addition, families, communities

and health workers have been known to disregard or discourage men during pregnancy.[11,16] In South Africa (SA), male partner involvement during and after pregnancy is exacerbated by the diversity in family arrangements and household structures that are intensified by racially differentiated levels of poverty and unemployment.[17] For example, poor African children are the least likely to live with their biological father, mainly as a result of men's lack of economic resources and social capital, as well as cultural norms.[17] Despite being the majority population group, poverty and unemployment are highest in the African population, while mean annual expenditure is lowest.[18] Not only can these financial difficulties lead to economic migration and family separation, but the inability to provide for one's family can result in poor mental health and negative health outcomes for men, which have a ripple effect on women and children.[19]

High levels of inequality also apply to healthcare utilisation, with only 17% of the African population accessing private healthcare at first sign of illness[18] and 10% having private medical insurance.[20] Unlike the private health system, public clinics and hospitals generally cannot accommodate men in the delivery room. Therefore, the majority of men cannot accompany and support their partner during birth. Cultural beliefs and practices can also influence father involvement, particularly in a multicultural country such as SA, where there are a number of different socioreligious orientations, e.g. the Zulu traditional religion, the Xhosa traditional religion, Hinduism, Islam and Christianity. In many southern African cultures, men are not recognised as the legitimate father of a child until financial requirements are met, which can lead to father-child non-residency, restricted visitation and involvement.[21] In the Islamic culture, premarital intercourse is forbidden and couples must be married before reproduction can take place.[22] This is likely to be a contributing factor to why the Indian population has the highest rate of co-residency.[17] Additional barriers to father involvement include incarceration, unusually low national marriage rates, high rates of informal kinship care and high levels of domestic violence.[3] These barriers not only limit men and the support they can provide to the mother, but have a negative impact on them as fathers.[23] Although many of these barriers require long-term political, social and economic solutions, in the short term, men should be provided with tailor-made messages, particularly acknowledging the importance of their involvement for child development and growth, maternal health and their own mental and emotional health.

Following guidelines from the World Health Organization (WHO), the South African National Department of Health (NDoH) adopted the practice of eight antenatal care visits during a pregnancy.[12] Included in these eight visits is the recommendation of an ultrasound scan at <24 weeks' gestation in a district hospital.[24] These routine health checks provide important opportunities to involve male partners and raise awareness of the importance of their involvement in their child's development. This article aims to describe and explore men's experiences of attending an early pregnancy ultrasound scan in SA.

Methods

Study design

This study is embedded in a randomised control trial (RCT) that compares the effects of an enhanced ultrasound experience on early childhood development with standard practice of care. Recruited women were blindly randomised through computer-generated randomisation to the intervention or control arm by the study research assistants, and both groups received an ultrasound examination as part of routine antenatal care. The control group received standard practice of care while the intervention group received the enhanced ultrasound with messages to promote early child development, an educational baby book and a printed and electronic image of their ultrasound scan. Mothers in both the intervention and control groups were encouraged to bring the father of the baby with them. Full details of the trial methods and recruitment procedures can be found in Richter *et al.*'s[25] article.

Setting

The study was performed in Soweto, home to 43% of the city of Johannesburg's population.[26] The trial was done in a research unit at Chris Hani Baragwanath Academic Hospital (CHBH), a tertiary hospital that attends to >22 000 births annually.

Participants

Women were recruited through the Fetal Medicine Unit (FMU) at CHBH, and were eligible for participation if they lived in Soweto, were ≥18 years of age and presented with a singleton pregnancy of <25 weeks' gestation. Women among whom major fetal abnormalities or severe maternal morbidities were detected were excluded from the study, but remained in clinical care at CHBH.

The participants in this study were men attending the ultrasound examinations with their partners. All men who attended were eligible, providing they were ≥18 years old.

Procedures

All participants completed individual questionnaires on information of their relationship status, experiences of the ultrasound scans and their level of anxiety before and after the procedure. All participants also completed the antenatal attachment scale.[27-29] The scale, designed to measure feelings, attitudes and behaviours specifically towards the fetus, has been validated for use among men and women. The male version is a 16-item questionnaire, while the female version is a 19-item questionnaire. A number of the ultrasound examinations where a partner attended were filmed to record the reactions, emotions and experiences of the participants in more detail. Data were collected between March and September 2019.

Data analysis

Data were analysed using Stata, version 14 (StataCorp., USA). Descriptive data are presented as frequencies and proportions. Open-ended questions were coded based on recurring themes and transformed into categorical variables. Responses to open-ended questions are presented qualitatively to report on the men's experiences.

Ethical approval

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, SA (ref. no. M181915). An amendment was approved by the University of the Witwatersrand to film some of the ultrasound appointments. Permission was obtained from CHBH to conduct the study. The trial is registered through the Pan African Clinical Trials Registry (ref. no. PACTR201808107241133). Participants provided written consent and were given a unique study identifier to maintain confidentiality. The participants who had their ultrasound appointments recorded provided additional written consent, allowing the procedure to be filmed. The study adheres to CONSORT guidelines.

Results

Sociodemographic characteristics

The sociodemographic characteristics of the partners are shown in Table 1. Of 249 mothers who attended the ultrasound examinations, 102 men accompanied their partner. The mean age of the men was 35 years, with the oldest being 56 years and the youngest 20 years. Only 32% of the men were reported to be living with the mothers, while a further 60% were married or in a committed relationship, but not living together. The remaining men were not in a relationship with the pregnant women (8%).

Table 1. Demographic characteristics of the baby's father

Demographic characteristics	*n* (%)
Age, years	
18 - 25	8 (7.84)
26 - 35	49 (48.00)
36 - 45	34 (33.33)
>45	11 (10.78)
Relationship status	
Not in a committed relationship	8 (7.84)
Married or in a committed relationship (living together)	33 (32.35)
Married or in a committed relationship (not living together)	61 (59.80)

Antenatal attachment

Prior to the ultrasound scan being conducted, the men were asked a range of questions regarding their attachment to the developing baby (Table 2). Ten percent of the men stated that they had not thought about the developing baby at all in the previous 2 weeks, compared with 55% who had thought about the baby almost all the time. Nearly all the men (89%) had positive feelings towards the developing baby, but a small number (3%) reported having negative feelings. Similarly, 97% of the men believed they would feel love and affection towards the baby after the birth, with 3% of the men expecting to feel some form of dislike towards the baby. One participant stated that he would be pleased if the pregnancy was lost.

Table 2. Antenatal attachment to the developing baby

Antenatal attachment	*n* (%)
Over the past 2 weeks I have thought about the developing baby	
Not at all	10 (9.80)
Occasionally	17 (16.67)
Frequently	14 (13.73)
Very frequently	5 (4.90)
Almost all the time	56 (54.90)
My feelings towards the developing baby over the past 2 weeks	
Very negative	1 (0.98)
Mainly negative	2 (1.96)
Mixed positive and negative	8 (7.84)
Mainly positive	12 (11.76)
Very positive	79 (77.45)
Over the past 2 weeks I have thought about what the baby looks like in the womb	
Not at all	6 (5.88)
Occasionally	7 (6.86)
Frequently	6 (5.88)
Very frequently	13 (12.75)
Almost all the time	70 (68.63)
What I expect to feel when I first see my baby after birth	
Mostly dislike	1 (0.98)
Dislike about quite a few aspects of the baby	1 (0.98)
Dislike about one or two aspects of the baby	1 (0.98)
Mostly affection	24 (23.53)
Intense affection	75 (73.53)
How I would feel if this was the last pregnancy	
Very pleased	1 (0.98)
Moderately pleased	-
Neutral	-
Moderately sad	1 (0.98)
Very sad	100 (98.04)

Ultrasound experiences

The results of the ultrasound experience questionnaire are shown in Table 3. All the men reported seeing a picture of the baby during the ultrasound scan, although 12% stated that the picture was unclear. Ninety-seven percent of the men felt comfortable asking questions during the scan and the majority (93%) understood what they saw in the picture, but 6% needed help to understand. There were not many suggestions for improvement of the scan, but included a bigger screen, a 3D image or a colour image.

In terms of how attending the ultrasound examination affected their feelings towards the baby, 95% of the men reported a positive effect, with only 5% reporting that there was no impact. Positive comments from the men included feeling happy, excited and more love towards the baby. One of the men, aged 28 years, stated:

> '... it made me feel happy because I saw the baby is developing well. The best part is when I heard the baby's heartbeat.'

When asked how attending the ultrasound scan affected their relationship with their partner, 21% stated that there was no change, while 28% and 19% of the men, respectively, reported having a stronger bond and a goal to be more supportive towards the mother. Feedback from a 28-year-old man included:

> 'I feel like it stirred up a feeling of oneness and a positive bond. There was a change in atmosphere between us.'

Another man, aged 34 years, stated:

> 'It made me closer to her. I didn't care [before], now I have changed and I will help and support her in every way.'

Finally, the men were asked about how the ultrasound scan had affected their expectations of becoming a father. Thirty percent reported that they were excited or ready to be a father, while 13% stated that it made them want to support their child. Additional feedback included that they wanted to be more responsible. A participant, aged 25 years, stated:

> 'I must be responsible and give time to my child and I have to participate in school. I will also save for my child. The growth of my child is very crucial. I must give him time and love, determination and raise the child with enthusiasm and energy.'

Partner anxiety

The men were asked about the anxiety they were feeling before and after the ultrasound scan.

Table 3. Ultrasound experiences

Experiences	*n* (%)
Did you feel welcome to ask questions?	
Yes	99 (97.06)
No	3 (2.94)
Did you see a picture of the baby?	
Saw nothing at all	-
Saw an unclear picture	12 (11.76)
Saw a clear and distinct picture	90 (88.24)
Did you understand what you saw in the picture?	
Did not understand	1 (0.98)
Needed more help to understand	6 (5.88)
Understood what I saw	95 (93.14)
Can you suggest any improvements?	
No	92 (90.20)
3D ultrasound	4 (3.92)
Colour image	1 (0.98)
Keep a video	1 (0.98)
Bigger screen	3 (2.94)
Keep a picture	1 (0.98)

Before the scan, 64% of the men reported feeling very anxious. After the scan, 54% still reported high levels of anxiety and 2% reported an increase in anxiety. The proportion reporting no anxiety increased from 26% before to 41% after. None of the men who experienced no anxiety before the ultrasound scan reported a rise in anxiety after the procedure.

Discussion

Attendance by men at antenatal ultrasound examinations in the public health sector in SA is low, as highlighted in this study, where <50% of the mothers were accompanied by their partner, even with encouragement and despite the service being offered on a weekend to remove conflicts with work schedules often cited as a reason for non-attendance.[15] Additional reasons why male attendance was low could be the number of non-cohabiting couples and cultural practices. For the couples who did attend together, only 32% reported living together, while 17% of married couples were not living together. With only 36% of children in SA reported as living with their biological father,[30] it is common for men not to live with their wives or children. Reasons include living away for work, divorce or repartnering, cultural practices and incarceration.[3] Within the African community, cultural practices in particular can act as a major barrier to male involvement both during pregnancy and throughout a child's life. Some ethnic groups prescribe only women to be present in the delivery room[31] and it has been reported that men are turned away or forbidden to attend by hospital staff.[32] A study in Tshwane, SA, found that only 18% of participants were allowed to bring their partner into the delivery room while giving birth and 59% chose to give birth alone because of cultural customs.[33] Before birth, women and men are sometimes separated[34] and families may deny unmarried fathers access to their child or partner until payment of *inhlawulo* (damages) or marriage takes place.[21] Such practices during pregnancy and birth may deter men from being involved to support their partners and add to some of the barriers already faced. There is a need to fully understand the reasons and barriers limiting men from attending antenatal health visits, be it culture, social or economic, to address these issues and improve male involvement during pregnancy, birth and throughout the child's life.

Attending the ultrasound examination had a positive impact on the majority of men in this study, affecting their relationship with the mother and baby. In line with previous studies, positive changes towards their partner included a stronger bond and feelings of love and togetherness.[6-8,23] A number of men also mentioned wanting to ensure increased support of the mother and child as a result of the ultrasound scan, a similar finding to that of Harpel and Barras,[5] who stated that partner attendance at an ultrasound examination is a means to enhance the support system of a pregnant woman. However, not all of the men reported positive changes as a result of attending the scan. This finding could be linked to their level of antenatal attachment. Although many of the men reported having positive thoughts and expected to feel affection towards their child, a few did not and one stated that he would be pleased should the pregnancy be lost. It would be beneficial to explore why these men feel as they do and to assess whether low antenatal attachment hinders male involvement and negatively affects the child. However, the scan was a positive experience for the majority of the men and there is a need for health services in SA to support male attendance and ensure that health facilities are male friendly. Additional interventions such as Healthy Pregnancy, Healthy Baby are needed to encourage more men who utilise the public health system to be involved from conception.

The research regarding paternal mental health has been limited, even though it has been acknowledged as an important factor to consider and is beginning to gain more interest.[35,36] In this study, we examined the anxiety levels of the men before and after the ultrasound procedure. Although levels of anxiety decreased for a number of men after the procedure, for 2% it increased and for 52% it remained high. The antenatal period can be a vulnerable time for men,[37] as they may have fewer support systems and choose not to share their emotions or problems.[38,39] For first-time fathers, navigating the transition to fatherhood may be a difficult time and for many of the men, anxiety may arise owing to concern about supporting their child financially.[35] This may be particularly relevant in SA, where there are high levels of unemployment, poverty and inequality. Anxiety in expectant fathers has also been found to be associated with their experience of depression[37,40] and can affect their parenting skills and social relationships.[40] With limited information on paternal mental health in SA, there is a need to not only determine the rates of paternal depression, but investigate whether depression, anxiety and antenatal attachment are associated. It is also important to explore how men's mental health problems influence father involvement and impact child development.

Study strengths and limitations

To our knowledge, this study is the first to actively include men during pregnancy ultrasound scans in the SA public healthcare system and it provides useful and encouraging evidence to further promote male attendance at antenatal health visits. However, some limitations were apparent. The first was the small sample size of the male partners who attended the study ultrasound scans. Although we provided personal invitation cards and offered the service on a weekend to overcome work or distance barriers, attendance remained low. This indicated additional barriers to male involvement and it would be useful to explore these further. Furthermore, the men who did attend may not be representative of the whole population who utilise the public health service, as they may be more likely already to be supportive of their partners, leading to potential bias towards positive experiences and responses.

Conclusions

The results of this study highlight that male attendance at prenatal ultrasound examinations has a positive effect, not only on the male

partner and their thoughts towards the pregnancy, but also towards their forthcoming child and their relationship with and support of their partner. Antenatal attachment among men was high and there was decreased anxiety among some men after the ultrasound scan. Health services in SA should accommodate fathers or male partners and encourage them to attend antenatal healthcare, including pregnancy ultrasound scans. Interventions such as Healthy Pregnancy, Healthy Baby can support the SA healthcare system and address individual, familial, societal and structural barriers to father involvement in long-term maternal and child care. Additional research is needed to determine the prevalence of ante- and postnatal depression in fathers, and how it affects child development and father involvement.

Declaration. None.

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Author contributions. RED analysed the data and wrote the manuscript. WS, TM and LMR provided substantial contributions and approved the final version for publication. All authors read and approved the manuscript.

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Training, confidence and knowledge of healthcare workers with regard to HIV and infant feeding in eThekwini, South Africa

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Background. Healthcare workers play an important role in educating mothers living with HIV regarding appropriate infant and young child feeding (IYCF) practices. However, it is not known if healthcare workers in eThekwini, KwaZulu-Natal (KZN), have been adequately trained regarding IYCF in the context of HIV and how knowledgeable and confident they are.
Objectives. To assess the training, confidence and knowledge of healthcare workers regarding IYCF in the context of HIV.
Methods. This was a descriptive cross-sectional study, which used a self-administered questionnaire developed for this survey. Healthcare workers (*n*=188), primarily doctors and nurses in antiretroviral, antenatal and paediatric departments at three regional hospitals (Addington Hospital, Prince Mshiyeni Memorial Hospital and RK Khan Hospital) in eThekwini, KZN, participated.
Results. Only 47.3% (*n*=89) of the participants had attended formal training on IYCF in the context of HIV. Most participants (*n*=171; 91.4%) felt they required more training. The mean overall confidence score of the group was 4.54 (standard deviation (SD) 1.28)%. The mean knowledge score of participants regarding IYCF in the context of HIV was 51.7%. The attendance of training did not equate to improved knowledge scores.
Conclusions. Although the healthcare workers were confident with counselling on IYCF in the context of HIV, their knowledge levels were lower than expected. This could be attributed to a lack of training or outdated or inefficient training. There is a need to improve the coverage and quality of IYCF and HIV training. Training courses should address behaviour change and test for understanding.

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Breastfeeding is recognised globally as the single most effective survival strategy for children <5 years of age.[1] Breastfeeding has protective effects against pneumonia, diarrhoeal disease and malnutrition.[2] The current infant and young child feeding (IYCF) policy in South Africa (SA) strongly recommends exclusive breastfeeding for the first 6 months of an infant's life, followed by the introduction of appropriate complementary foods with continued breastfeeding until ≥2 years of age.[3,4] This recommendation not only applies to infants and young children in the general population, but also to those of mothers living with HIV.[4] Furthermore, it is in alignment with the 2016 World Health Organization (WHO) guideline on HIV and infant feeding.[2] There is a low risk of HIV transmission from mother to child through breastmilk, with a risk of 0.19% per month in the case of diligent antiretroviral therapy (ART) use.[5] It is clear that the benefits of breastfeeding outweigh the risk of HIV transmission.[2]

However, breastfeeding was not always encouraged for mothers living with HIV. Many changes have been made to the SA prevention of mother-to-child transmission (PMTCT) of HIV programme over the years, including changes to the IYCF recommendations.[4,6,7] Some of these changes include whether mothers living with HIV should breastfeed or not; the duration of breastfeeding; whether mothers should abruptly or gradually stop breastfeeding; and which ART drugs mothers living with HIV should receive.[4,6,7] Ongoing changes to guidelines have the potential to confuse healthcare workers.[8,9] Several African studies found that healthcare workers have poor knowledge regarding IYCF guidelines in the context of HIV.[9-12] This is of concern, as mothers living with HIV require clear, up-to-date and consistent IYCF messages and support.[13] However, it is not known if healthcare workers in eThekwini, KwaZulu-Natal (KZN), have been adequately trained in IYCF in the context of HIV and how knowledgeable and confident they are. Therefore, the aim of this study was to assess the training, knowledge and confidence of healthcare workers, primarily doctors and nurses, employed at eThekwini, KZN regional state hospitals' antiretroviral (ARV), paediatric and antenatal departments, regarding IYCF in the context of HIV.

Methods

Study design and setting

This descriptive cross-sectional study was conducted between July and December 2018 at three eThekwini regional hospitals (Addington Hospital, Prince Mshiyeni Memorial Hospital and RK Khan Hospital). Data were collected intermittently over this period and the days chosen for data collection varied between the different hospitals and departments, depending on the availability of healthcare workers.

Study population and sample selection

Only permanently employed medical officers, medical registrars, medical consultants, enrolled nurses, professional nurses and other healthcare workers at the three hospitals' ARV, paediatric and antenatal departments were considered for inclusion in the study. A convenience sample was used, as only those healthcare workers who met the inclusion criteria and were on duty on the days of data collection were invited to participate in the study.

Self-administered questionnaire

A self-administered questionnaire with primarily closed-ended questions was developed for the study. The questionnaire was based on recommendations included in the National Department of Health (NDoH) 2013 *Infant and Young Child Feeding Policy*,[3] the 2017 *Amendment of the 2013 Infant and Young Child Feeding Policy*[4] and the 2015 *National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults*.[6]

A panel of experts reviewed the questionnaire to ensure content validity. The questionnaire consisted of 8 sections: (*i*) demographic information; (*ii*) training on HIV and IYCF; (*iii*) counselling on HIV and IYCF; (*iv*) confidence to counsel mothers living with HIV on different aspects of IYCF; (*v*) knowledge of IYCF; (*vi*) knowledge of risk of HIV transmission; (*vii*) understanding of key terms, determining ART compliance and recommendations; and (*viii*) opinions on guidelines, compliance and practices. However, responses to sections (*iii*) and (*viii*) are not reported in this article.

The confidence section involved participants' ranking of how confident they felt counselling mothers living with HIV on IYCF principles in 14 different scenarios. This was assessed using a 6-point Likert scale, where 1 = not at all confident and 6 = very confident. An overall knowledge score was given to the participants by combining the scores from the knowledge questions. The first knowledge section included 17 true/false questions, which tested knowledge of different IYCF principles. The second knowledge section included 4 multiple-choice questions regarding the risk of HIV transmission through breastfeeding in different scenarios. The final knowledge section included open-ended questions.

The first open-ended question asked participants what they understood by the term 'exclusive breastfeeding'. The WHO defines exclusive breastfeeding as 'providing breast milk without any liquids or solids, not even water, except for oral rehydration solution or drops or syrups of vitamins, minerals or medicines'. This definition was divided into 3 components for scoring the answers: (*i*) an infant receives only breastmilk; (*ii*) no other liquids or solids; and (*iii*) with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines. If an answer included all 3 components of the definition, this was scored as 'excellent' knowledge and given a score of 100%. If an answer included the first and either of the other components, this was scored as 'good' knowledge and given a score of 66.7%. If only the first component was mentioned, the answer was scored as 'average' knowledge and given a score of 33.3%. If the respondent's answer was completely inappropriate, their knowledge was scored as 'poor' and they were scored 0%.

The second open-ended question asked participants what they understood by the term 'treatment failure'. Treatment failure is defined by the *National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults*[6] as 'a persistently detectable viral load ≤1 000 copies/mL, i.e. 2 consecutive viral load measurements within a 2-month interval, with adherence support between measurements, after at least 6 months of using ART drugs'.[6] Participants' answers were scored out of 3. If their answer included having multiple (≥2) persistently high viral load readings after using ART for at least 6 months with good adherence, their answer was scored as 'excellent' and a 100% score was awarded. If their answer included having multiple (≥2) persistently high viral load readings after using ART for at least 6 months, but adherence was not mentioned, their answer was scored as 'good' and they were given 66.7%. If their answer only mentioned the patient being on ART, but still having a high viral load, their answer was scored as 'average' and they were awarded 33.3%. Incorrect answers, those that did not mention the use of ART or those that mentioned poor adherence as a cause of treatment failure were scored as 'poor' and given 0%.

The third open-ended question asked participants to briefly describe how they would determine ART compliance in pregnant/lactating women living with HIV. Strategies to assess ART compliance mentioned in the *National Antiretroviral Treatment Guidelines*, 2004, include: (*i*) blood tests; (*ii*) ARV pill-returns count; (*iii*) routine adherence discussions (self-reports); and (*iv*) attendance of follow-up visits.[14] Answers that included any of these methods or any other acceptable methods for determining ART compliance (such as clinical assessments) were scored as 'correct' and given 100%. Incorrect answers were given 0%.

The last open-ended question asked when participants would recommend that a mother living with HIV stops breastfeeding. The IYCF policy in SA recommends that mothers living with HIV should continue breastfeeding for 24 months.[3,6] Therefore, it is recommended that these mothers should discontinue breastfeeding at 24 months. However, the guideline also recommends that pregnant and breastfeeding mothers, who have confirmed treatment failure, should not breastfeed their infants owing to the increased risk of mother-to-child transmission, with poor viral suppression. Other medical contraindications for breastfeeding are also listed in the IYCF policy.[3] Answers that included any of the abovementioned scenarios as an appropriate time to recommend a mother to stop breastfeeding were accepted as correct, and the respondent was scored 100% for their answer. Answers that included incorrect and correct information were considered partially correct and scored 50%. Incorrect answers were given 0%.

Data analysis

Responses to the knowledge questions were scored using the recommendations included in the NDoH 2013 IYCF policy,[3] the 2017 amendment of the IYCF policy[4] and the 2015 consolidated guidelines for PMTCT and the management of HIV in children, adolescents and adults.[6] Unanswered questions that investigated knowledge were scored as incorrect. Data were entered into Microsoft Excel (Microsoft Inc., USA) by the researcher and cross-checked by a research assistant to ensure accuracy in data capture. Data were analysed using SPSS, version 22 (IBM Corp., USA). Descriptive statistics, i.e. frequencies and percentages for categorical data and medians and percentiles for continuous data, were calculated. Relationships between variables were calculated and described using 95% confidence intervals (CIs) for differences in medians or percentages. A p-value of <0.05 was considered significant.

Ethical approval

Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KZN (ref. no. HSS/0296/018M), as well as from the Research Committee, KZN Department of Health (ref. no. HRKM129/18). All participants gave written consent prior to answering the questionnaire. The researcher informed the participants that their participation was voluntary and anonymous, that there were no risks associated with participation and that there would be no remuneration for participation.

Results

Eligible doctors and nurses on duty on data collection days were used to calculate the response rate for the study. The total response rate was 82.2% (n=175). Thirteen other eligible healthcare workers from other departments or professions also participated in the study.

However, they were not included in the response rate calculation, as it was not known how many of them were on duty on the data collection days. This resulted in a total number of participants of 188, some of whom did not answer all questions; the missing data are reported. Table 1 presents the sample characteristics. Just over 81% of the sample (*n*=154) were female, with 18.1% (*n*=34) male. The largest group of participants was between 31 and 45 years old (54.3%; *n*=102). Seventy (37.2%) professional nurses participated in the study, followed by 44 (23.4%) enrolled nurses and 36 (19.1%) medical officers. Equal numbers of participants (46.8%; *n*=88) had <5 years' experience and between 5 and <20 years of experience, respectively. The majority of participants worked in the paediatrics department (52.7%; *n*=99), followed by the antenatal department (29.8%; *n*=56).

Training

More than half of the participants (*n*=97; 51.6%) indicated that they had not been formally trained on IYCF in the context of HIV (Table 2). Of the 89 who indicated that they had attended training, 67 (75.3%) had attended the NDoH 3-day ICYF training (an adaptation of the Baby-friendly Hospital Initiative (BFHI) training course developed by the WHO and United Nations Children's Fund (UNICEF)).[15] Twenty participants (22.5%) indicated that they had been trained as part of their formal degree or diploma and 16 (18.0%) that they had received 'other' training. Only 36 (40.4%) of the 89 who had attended IYCF training specified that they had received training during the previous 2 years. One hundred and seventy-three participants (*n*=92.0%) indicated a need for further training on HIV and IYCF guidelines.

Table 1. Sample characteristics, *n*=188

Characteristics	*n* (%)
Gender	
Male	34 (18.1)
Female	154 (81.9)
Age, years*	
22 - 30	23 (12.2)
31 - 45	102 (54.3)
46 - 55	40 (21.3)
>55	22 (11.7)
Professional rank*	
Medical officer	36 (19.1)
Medical registrar	8 (4.3)
Medical consultant	19 (10.1)
Professional nurse	70 (37.2)
Enrolled nurse	44 (23.4)
Enrolled auxiliary nurse	7 (3.7)
HIV counsellor	2 (1.1)
Experience, years*	
<5	88 (46.8)
5 - <20	88 (46.8)
≥20	11 (5.9)
Department*	
Paediatrics	99 (52.7)
Antenatal	56 (29.8)
Antiretroviral	30 (16.0)
Other	2 (1.1)

*Some participants did not answer all questions; therefore, percentages do not add up to 100%.

Confidence

Participants were asked to rank how confident they were with counselling mothers living with HIV regarding IYCF principles in different scenarios (Table 3). The majority of participants were found to be confident in all counselling scenarios and the mean overall confidence score for the group was 4.54 (standard deviation (SD)1.28)%.

Knowledge

The participants scored a mean of 63.5 (14.6)% for the true/false questions. For the section pertaining to the risk of transmission, the participants had a mean score of 26.7 (25.3)% (Table 4). For the open-ended questions, the participants scored a mean of 52.7 (25.8)% for the definition of exclusive breastfeeding; a mean of 26.3 (34.4)% for the understanding of treatment failure; a mean of 69.3 (46.3)% for determining ART compliance in pregnant/lactating women living with HIV; and a mean of 34.7 (46.7)% for when a mother living with HIV should stop breastfeeding.

The mean knowledge score of the participants was 51.7 (14.1)% (Table 5). No significant relationship was found between the attendance of training and mean knowledge scores (p=0.217).

Discussion

According to the WHO, a clear and well-supported policy, coupled with appropriate training of healthcare workers, is of upmost importance for the successful implementation of an IYCF policy.[16] Despite SA having a comprehensive IYCF policy that states clear guidelines regarding HIV, this study shows that the majority of healthcare workers were insufficiently trained in the HIV component of this policy. This result was unexpected, as all three facilities were Mother-Baby-Friendly Initiative accredited (an adaptation of the BFHI) at the time of the study. This accreditation requires that a minimum of 80% of clinical staff who are in contact with mothers and/or infants must have attended the 3-day IYCF training course offered by the NDoH.[17] The lack of IYCF and HIV training has proven to be a recurrent issue in other African studies.[18-21] This is of concern, as it is essential for healthcare workers to be equipped with the necessary knowledge needed to successfully implement IYCF policies and provide appropriate counselling to mothers.[18] An additional concern is that, in the current study, the healthcare workers who had undergone training were not significantly more

Table 2. Training received by participants, *n*=188

Training	*n* (%)
Attendance of training, *n*=188*	
Yes	89 (47.3)
No	97 (51.6)
Type of training, *n*=89*	
3-day IYCF	67 (75.3)
Part of degree/diploma	20 (22.5)
Other	16 (18.0)
Year last trained, *n*=89*	
2016 - 2018	36 (40.4)
Before 2016	35 (39.3)
Further training required, *n*=188*	
Yes	173 (92.0)
No	15 (8.0)

IYCF = infant and young child feeding.
*Some participants did not answer all questions; therefore, percentages do not add up to 100%.

Table 3. Counselling confidence of participants, *n*=181*

Counselling scenario	*n* (%) Not at all confident 1	2	3	4	5	Very confident 6	Mean (SD)
Counselling an expectant mother living with HIV on the benefits of exclusive breastfeeding for 6 months	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.73 (1.60)
Counselling an expectant mother living without HIV on the benefits of exclusive breastfeeding for 6 months	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.91 (1.51)
Counselling an expectant mother living with HIV on the importance of skin-to-skin contact after birth	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.92 (1.53)
Counselling a mother on breastfeeding positioning and attachment	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.77 (1.54)
Counselling a mother on how to identify hunger cues in her infant	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.59 (1.59)
Counselling a mother living with HIV on when to introduce complementary food to her infant	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	26 (14.4)	88 (48.6)	4.63 (1.52)
Counselling a mother on which complementary foods to give to her infant and when to give these foods	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	26 (14.4)	88 (48.6)	4.41 (1.62)
Counselling a mother living with HIV on expressing breastmilk	13 (7.2)	5 (2.8)	27 (14.9)	17 (9.4)	28 (15.5)	89 (49.2)	4.62 (1.59)
Counselling a mother living with HIV on safe formula preparation	13 (7.2)	4 (2.2)	27 (14.9)	17 (9.4)	27 (14.9)	89 (49.2)	4.52 (1.69)
Advising a mother living with HIV on the management of breast engorgement	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	27 (14.9)	88 (48.6)	4.32 (1.53)
Advising a mother living with HIV on the management of cracked nipples	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	26 (14.4)	88 (48.6)	4.34 (1.54)
Advising a mother living with HIV on the management of mastitis	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	27 (14.9)	88 (48.6)	4.11 (1.61)
Counselling a mother with diagnosed ARV treatment failure on her infant feeding options	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	27 (14.9)	89 (49.2)	4.22 (1.64)
Counselling a mother living with HIV on ART adherence for both herself and her infant	12 (6.6)	5 (2.8)	27 (14.9)	17 (9.4)	27 (14.9)	89 (49.2)	4.72 (1.54)
Overall confidence score							4.54 (1.28)

SD = standard deviation; ARV = antiretroviral; ART = antiretroviral therapy.
*Some participants did not answer; therefore, *n*=181.

Table 4. Answers given by the sample participants regarding the risk of transmission in different scenarios

Feeding practice	ART	Overall risk of transmission at 6 months, %	Participants who selected each of the answers correctly, *n* (%)* <5%	5 - 20%	21 - 40%	41 - 60%	>60%
Exclusive breastfeeding	No maternal ART	1.42	46 (24.5)	43 (22.9)	21 (11.2)	34 (18.1)	31 (16.5)
Mixed feeding	No maternal ART	2.35	10 (5.3)	32 (17.0)	39 (20.7)	35 (18.6)	61 (32.4)
Exclusive breastfeeding	Mother on ART	1.13	109 (58.0)	27 (14.3)	20 (10.6)	11 (5.9)	10 (5.3)
Mixed feeding	Mother on ART	1.13	36 (19.1)	42 (22.3)	41 (21.8)	22 (11.7)	36 (19.1)

ART = antiretroviral therapy.
*Percentages do not add up to 100%, as some participants left answers blank (blank answers were included in the analysis but were scored as 'incorrect').

knowledgeable than those who had not been trained. Of the participants who received training in this field, three-quarters received training through the 3-day training course offered by the NDoH. This begs us to question the efficacy of this initiative. Moreover, it may be relevant that of the participants who attended the NDoH 3-day IYCF training course, just >40% had done so within the previous 2 years, which may have possibly contributed to the poor knowledge demonstrated. It is likely that these participants may have forgotten a significant amount of what they had learnt or that the training content was outdated.

Healthcare workers in ARV, paediatric and antenatal departments are responsible for the counselling of mothers living with HIV regarding IYCF.[17] A study by Horwood *et al.*[22] found that SA mothers living with HIV diligently followed the IYCF advice given by healthcare workers, and perceived healthcare workers to be knowledgeable professionals who provide accurate advice. If healthcare workers are not knowledgeable about IYCF, it is likely that they will share incorrect messages with mothers, which in turn could lead to poor IYCF practices.[22] The healthcare workers in the current study were not considered to be adequately knowledgeable about IYCF in the context of HIV, with a mean knowledge score of only 51.7%.

Many participants grossly overestimated the risk of HIV transmission through breastfeeding. This may be due to early

Table 5. Overall knowledge regarding IYCF and HIV

Knowledge	Knowledge score, mean (SD), %
Multiple-choice questions regarding knowledge of IYCF	63.5 (14.6)
Risk of transmission	26.7 (25.3)
Understanding of exclusive breastfeeding	52.7 (25.8)
Understanding of treatment failure	26.3 (34.4)
Determining ART compliance	69.3 (46.3)
When a mother should stop breastfeeding	34.7 (46.7)
Total	51.7 (14.1)

IYCF = infant and young child feeding; SD = standard deviation; ART = antiretroviral therapy.

PMTCT guidelines, which encouraged mothers to formula feed their infants if they were able to.[2] Many of the participants incorrectly associated mixed feeding with the use of ART, with a much higher risk of HIV transmission. The belief that breastfeeding carries a relatively high risk of HIV transmission may cause healthcare workers to be less supportive of breastfeeding. More than half of the total number of participants estimated the risk of transmission to be >20%, much higher than the actual risk of 1.13%.[5] Although not relevant at the time of data collection, in 2019 SA adopted the WHO 2016 guiding practice statement, 'Mothers living with HIV and healthcare workers can be reassured that ART reduces the risk of postnatal HIV transmission in the context of mixed feeding. Although exclusive breastfeeding is recommended, practising mixed feeding with formula milk is not a reason to stop breastfeeding in the presence of ARV drugs.'[23] Increased awareness is likely needed regarding the effectiveness of ART in reducing the risk of HIV transmission through breastfeeding, including in cases of mixed feeding, before healthcare workers adopt this recommendation.

The participants had a poor understanding of the term 'exclusive breastfeeding', with a mean score of 52.7%, and only 8.5% of participants showed an excellent understanding of the term and 48.9% a good understanding. This is of concern, as these healthcare workers should be encouraging mothers living with HIV to exclusively breastfeed their infants for the first 6 months of life, as per the country's IYCF policy.[3] Without a proper understanding of the term, it is possible that inadequate or inaccurate information is shared with mothers. A similar study by Van Rensburg *et al.*[9] found that 70.0% of healthcare workers knew that exclusive breastfeeding meant that only breastmilk should be given, but only 6.7% of healthcare workers could comprehensively explain the term. However, they used a different definition for the term to that in the current study.[9]

In SA, confirmed treatment failure is a contraindication for breastfeeding due to the increased risk of mother-to-child transmission with poor viral suppression.[6] The participants in the current study had a very poor understanding of the term 'treatment failure'. Treatment failure can only be diagnosed in patients who are compliant with their ART. Yet, 35.5% of participants incorrectly described treatment failure as the occurrence of a high viral load because of poor adherence. With poor adherence, it would be expected that the viral load would not be adequately suppressed owing to insufficient ART rather than ineffective ART. If treatment failure is misdiagnosed, a healthcare worker may discourage a mother from breastfeeding her infant. The poor understanding of treatment failure is not only of concern with regard to IYCF, but for overall HIV management.

The participants scored poorly (34.7%) when asked when they would recommend a mother living with HIV to stop breastfeeding. It is a serious concern that many healthcare workers would encourage mothers to discontinue breastfeeding in cases where it is not contraindicated. Incorrect answers frequently given included 'at 6 months' and 'at 1 year'. These answers may have been given as a result of previous guidelines, which recommended these periods (6 months of breastfeeding was recommended in the 2008 PMTCT guideline, and prior to its 2017 amendment, the 2013 IYCF policy recommended breastfeeding until 1 year of age).[3,4,24] This illustrates a lack of awareness of or a lack of support for the current recommendations.

Overall, the healthcare workers in the study were found to be confident with counselling mothers living with HIV regarding IYCF practices. The more confident a healthcare worker is, the more effective they are at influencing a mother's feeding choice.[25] While it is reassuring to know that healthcare workers are confident with the counselling of mothers living with HIV regarding IYCF, it is a concern that they lack the accompanying knowledge. With high levels of confidence and poor IYCF knowledge, it is possible that these healthcare workers may be contributing to poor feeding practices of mothers living with HIV.

There is a need to improve the coverage of IYCF and HIV training in the three facilities, as well as the quality of training. Training courses should address behaviour change and test for understanding. Facilities need to ensure that guidelines, policies and updates are effectively disseminated to their healthcare workers and that these workers are accountable for the correct implementation of the relevant guidelines and policies. Further research is needed to determine which IYCF and HIV training strategies effectively improve knowledge levels.

Study limitations

The study was limited, as only three regional hospitals in eThekwini participated. These findings are not representative of all the healthcare workers in eThekwini and generalised conclusions cannot be drawn. In addition, many study participants were not supervised when completing their questionnaires owing to logistical limitations. It is possible that some participants could have discussed the questions with each other or looked up the answers. Another limitation was that, although efforts were made to avoid leading questions in the questionnaire, the use of predetermined questions might have introduced bias.

Conclusions

This study identified a lack of training regarding IYCF in the context of HIV among the healthcare workers who participated. Of particular concern is that the attendance of training was not associated with significantly higher knowledge scores. This study highlights a need for improved training on IYCF in the context of HIV at the three hospitals involved in the study. Although the healthcare workers in this study were found to be confident regarding HIV and IYCF counselling, their knowledge level was lower than expected, which could be attributed to a lack of training, outdated training or inefficient training. The coverage and quality of IYCF and HIV training need to be improved. Furthermore, training courses should address the application of knowledge and should test for understanding. Future research should investigate the effectiveness

of the different IYCF and HIV training strategies in improving knowledge levels. The impact of IYCF counselling of mothers living with HIV with regard to infant feeding decisions, should also be further investigated.

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Moderate to severe neonatal encephalopathy with suspected hypoxic-ischaemic encephalopathy in cooled term infants born in Tygerberg Academic Hospital: Characteristics of fetal monitoring and modifiable factors

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Background. In South Africa, in babies >2 500 g, intrapartum asphyxia is the main cause of neonatal death or stillbirth in those who were alive prior to labour. In a developing population, ~60% of neonatal encephalopathy (NE) has evidence of intrapartum hypoxic ischaemia. Therapeutic hypothermia for term babies born with NE can improve neonatal prognosis and long-term survival.
Objectives. To identify the healthcare worker- and system-related modifiable factor(s) that were associated with NE in babies of ≥36 weeks' gestation born at Tygerberg Hospital (a secondary/tertiary referral hospital) between 1 January 2016 and 30 December 2018.
Methods. This was an observational cross-sectional study analysing data from the Tygerberg Hospital Hypoxic Ischaemic Encephalopathy database, the electronic labour ward register, the mortality database and clinical data from patient folders.
Results. A total of 118 babies were admitted for head cooling, and therefore included in the study. The hospital in-born rate for serious encephalopathy is 5.5/1 000 in singleton live-born babies (9/1 000 rate for live-born deliveries ≥36 weeks). A sentinel event was identified in 19 (16%) cases. Delay in accessing theatre was the main system-related modifiable factor (25/58 or 43% of cases delivered by emergency caesarean delivery). The average decision-to-incision time was 1 hour 40 minutes, while the average bed occupancy in the emergency maternity centre was 102%. Failure to recognise or respond to an abnormal cardiotocograph was the dominant avoidable factor related to healthcare workers in 34 cases (36.4%).
Conclusion. Babies born with severe NE place a burden on parents, healthcare staff and resources. Careful intrapartum care, including utilisation of protocols for the use of oxytocin, are imperative. It is recommended that improved access to emergency theatres and appropriately trained staff for maternity units should be a priority for healthcare planners.

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Despite modern obstetric practice and a global increase in facility-based births, perinatal morbidity and mortality are still very high in low- to middle-income countries (LMICs). According to the United Nations Children's Fund, there were approximately 2.5 million neonatal deaths (deaths within the first month of life) in 2018, of which almost all occurred in LMICs.[1] In South Africa (SA), birth asphyxia plays a significant role in the perinatal death rate. In the category for term infants (>2 500 g), intrapartum asphyxia is the main cause of stillbirth in babies who were alive before the onset of labour, and the main cause of neonatal deaths.[2]

However, not all babies exposed to intrapartum asphyxia die. It is estimated that in a developing population, 60% of neonatal encephalopathy (NE) has some evidence of intrapartum hypoxic ischaemia.[3] With the increased availability and utility, even in low-resourced settings, of modern neuroprotective methods such as therapeutic hypothermia, there is improved prognosis and long-term survival of these neonates.[4] Children who survive an acquired neonatal brain injury live with a wide spectrum of neurological morbidity ranging from mild affectation to profound cerebral palsy. Even though therapeutic hypothermia may prevent cerebral palsy, emotional, cognitive and motor performance difficulties may become obvious in later childhood.[5] The morbidity that stems from hypoxic-ischaemic encephalopathy (HIE) imposes an immeasurable personal, social and financial cost on the survivor, their family, the healthcare system and society as a whole.[6,7] This forms the basis for justification of the massive medicolegal costs involved with litigation in these cases.

Reasons for these tragic outcomes are often sought in the obstetric sphere. Based on the national Perinatal Problem Identification Programme (PPIP) data of the 2014 - 2016 triennium for SA, there was no decrease in the percentage of babies who died secondary to intrapartum asphyxia.[2] This is despite 76% of women accessing antenatal care and 97% of women being delivered by qualified healthcare providers, therefore suggesting that the contributors to these outcomes are likely multifactorial and deserve scrutiny. Some of these factors extend beyond the control of healthcare workers: for example, no antenatal attendance, delay in transport to hospital, unexpected sentinel events such as cord prolapse or abruptio placentae, intrauterine infection or prematurity. Mothers who deliver at a tertiary/central hospital are referred for specific indications that usually infer underlying maternal risk factors. When delivered at Tygerberg Hospital, at or near term, the expectation is that high-quality care (which includes continuous fetal monitoring and quick access to theatre when indicated) will be available and provided.

Likewise, the baby should have access to a range of post-delivery interventions, including adequate resuscitation, access to high care or neonatal intensive care unit (NICU) and therapeutic hypothermia.

The aim of the present study was to undertake a detailed analysis of a narrowly defined group of babies with NE to determine which obstetric healthcare worker- and/or system-related modifiable factors potentially contributed to adverse neurological outcome.

Methods

This was an observational cross-sectional study using data from the routinely collected Tygerberg HIE database, electronic labour ward register, PPIP mortality database and clinical data from patient folders.

Setting and study population

The study included all infants at a gestation ≥36 weeks who were delivered at Tygerberg Hospital between 1 January 2016 and 30 December 2018 (a period of 36 months) and were referred to the NICU for therapeutic hypothermia. Babies are considered for this intervention when the following criteria are met: prolonged (≥10 minutes) need for resuscitation, and/or a pH ≤7 or base deficit ≥16 on cord gas or infant blood within an hour of birth. Additional clinical criteria to be met include moderate to severe encephalopathy, seizures or a Thompson HIE score[8] ≥10.[4]

Babies referred to the Tygerberg NICU from other institutions were excluded, as their prognosis would be influenced by transport availability and the quality of pre-hospital care. The other exclusion criteria were multiple pregnancies, congenital anomalies and congenital viral infection.

Tygerberg Hospital is a large regional and tertiary referral hospital for one-half of the metropolitan area of Cape Town and surrounding rural towns. It serves a predominantly poor socioeconomic population, and has an average of 7 600 deliveries annually. It was classified by the National Department of Health (NDoH) in 2012 as one of 10 central hospitals in SA.

Data analysis

Data were analysed using Excel 365 (Microsoft Corp., USA) and Stata 14 (StataCorp, USA). Demographic characteristics are described with summary statistics such as mean, standard deviation (SD) and range for quantitative variables.

Main outcome measurements

This audit utilised the same broad categories to measure avoidable (or modifiable) factors as are utilised in the SA national PPIP tool: patient-related, healthcare-related and systematic errors that preceded and probably contributed to the event. These are defined as incidents related to the actions of the mother, the healthcare worker or the health system that may have altered the outcome of the specific case had it been managed differently.[9]

Prolonged labour in the first or second stage was defined using the criteria in use at that time in SA (as published in the national Guidelines for Maternity Care in South Africa of 2016).[10] Poor progress in the first (active) phase of labour was defined when there was crossing of the 2-hour action line on the partogram after 4 cm cervical dilatation. Poor progress in the second stage of labour was defined when delivery had not occurred after 30 minutes of pushing (in a multigravida) or 45 minutes of pushing (in a primigravida).

For intrapartum events, the focus was on fetal monitoring during labour. Cardiotocographic traces were interpreted using the criteria of the National Institute for Health and Care Excellence (NICE)[11] as this is also the system of classification used in daily practice at Tygerberg Hospital. Traces were analysed by three specialist obstetricians, one of whom is a maternal fetal subspecialist. As this was part of the audit, they were not blinded to the outcome.

Definitions and measuring instruments

The bed occupancy rate was calculated as the ratio between the number of occupied beds (based on inpatient admission and discharge data) divided by the number of beds available, with the ratio multiplied by 100 to obtain a percentage.

TBH fetal growth charts were used to correlate gestational age and fetal weight.[12]

Delay in access to emergency theatre was measured as the difference between the time of incision and the time of decision in minutes. The hospital uses the Royal College of Obstetricians and Gynaecologists (RCOG) classification of urgency for caesarean delivery (CD),[13] and a delay of more than 30 minutes for life-threatening cases is regarded as significant at TBH.

Oxytocin for induction or augmentation of labour at TBH is governed by a strict protocol, with a high concentration/low volume dosage regimen starting at 2 milliunits (mU)/min with incremental increase up to a maximum of 20 mU/min. Oxytocin use was regarded as injudicious when there was gross deviation from the protocol, e.g. failure to stop the infusion during severe fetal distress.

The SA NDoH has not published staffing norms for maternity wards in regional or tertiary hospitals in SA, so any modifiable factors relating to staffing norms are mostly subjective. If vital or critical patient information was missed by a midwife, it is difficult to measure whether this was due to inexperience, genuine oversight or too few midwives on duty. For this reason, modifiable factors related to 'insufficient nurses on duty' were not measured, but coded under related items (e.g. fetal distress not detected).

Results

During the audit period there were 20 068 live-born babies in TBH, of whom 13 052 were at ≥36 weeks' gestation. A total of 118 babies met the criteria for this audit. This equates to a hospital in-born rate of 5.5/1 000 for serious encephalopathy in singleton live-born babies (9/1 000 rate for live-born deliveries ≥36 weeks' gestation only). As the rate excludes referrals and HIE cases delivered in hospitals outside of Tygerberg, it is not a population-based rate.

Twenty-three babies of ≥36 weeks' gestational age died intrapartum owing to severe asphyxia during the time of the audit. As the purpose of the audit was to identify modifiable factors in babies admitted for head cooling, these were not included in the audit, but the results are given here for completeness. Eight of these deaths were due to severe maternal disease (abruptio, severe pre-eclampsia, chorioamnionitis or attempted late abortion), with no healthcare worker-related modifiable factors. In the remaining 15 cases, modifiable factors were identified in 5 (fetal distress not detected in 3 cases and theatre delay in 2).

The mean (SD) age of the birth mothers was 26 (7) years. The median (range) gravidity was 2 (1 - 6) and the median (range) parity 0 (0 - 7). The mean (SD) birthweight of the babies in the study group was 3 086 (576) g.

The bed occupancy rate for the labour ward was 102% during the study period. The hospital CD rate for the study period was 46.4%, and there were 299 vacuum extractions, 312 breech deliveries and 43 forceps deliveries. The corresponding population-based CD rate (for the total hospital referral area) during this time was 25%. The methods of delivery of the study group are given in Fig. 1, showing a significantly higher percentage of instrumental deliveries (16.9% in the study group, v. 1.7% in the total hospital population, $p<0.001$).

For 8 cases (42%), a vacuum delivery was done for fetal distress as there was no immediate access to theatre. A further 9 vacuum-assisted delivers were done for poor progress in the second stage of labour, and 2 for maternal indications. The other delivery methods had a similar distribution to the general hospital.

All the women in the study were referred for specialist care during the antenatal or intrapartum period, and a number of underlying disorders were identified: hypertensive disease of pregnancy (*n*=56; 47%); morbid obesity (body mass index (BMI) ≥40 kg/m^2) in 27 women (23%); and overt diabetes (*n*=9; 7.6%). Some women had more than one underlying condition. Twenty women were HIV-positive (all of them on the standard fixed dose of three antiretroviral drugs).

For 73 (62%) of the pregnancies, accurate gestational age was available using early (<24 weeks) ultrasound. Plotting of the birthweight against the growth centiles for these babies reveals that 15% of babies weighed less than the 10th centile and 22% above the 90th centile. This is shown in Fig. 2. Fifty percent (*n*=7) of the 14 large-for-gestational-age babies were born to mothers with severe obesity (body mass index >40 kg/m^2), and a further 4 to mothers with diabetes in pregnancy.

A sentinel event was identified in 19 (16%) cases: 8 shoulder dystocia, 6 abruptio placentae, 3 cord prolapse and 2 cases of uterine rupture.

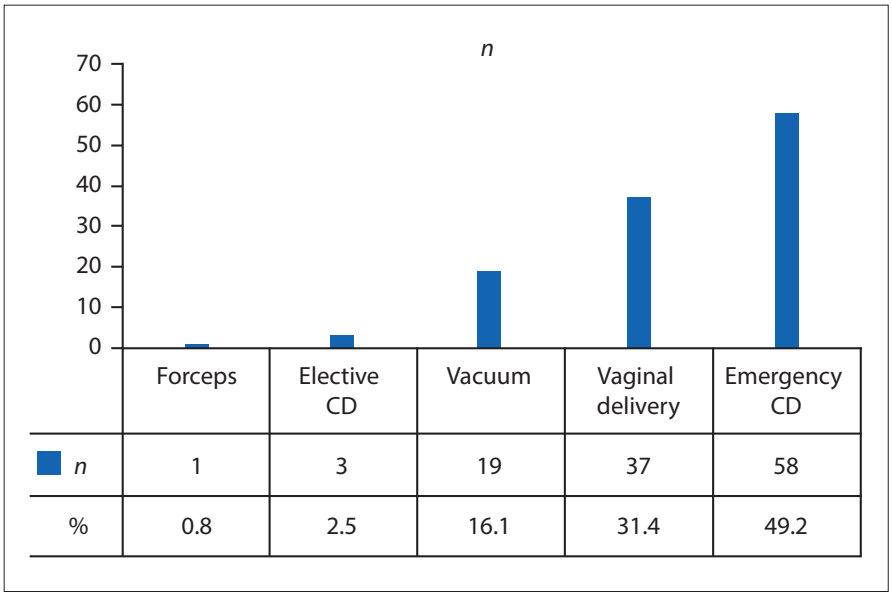
System-related modifiable factors were identified in 18 cases (Fig. 3). The main system-related factor that was deemed avoidable was a delay in getting a patient to theatre once the decision was made for an abdominal delivery (*n*=25/58 or 43% of cases delivered via emergency CD). The longest waiting time for theatre was 7 hours. This was due to the use of theatre to ventilate another patient until an intensive care unit bed became available. The shortest time interval was 20 minutes. However, on average, the waiting time (decision to incision) was 1 hour and 40 minutes.

The dominant avoidable factor related to healthcare workers was the failure to recognise or react to abnormal cardiotocograph (CTG) tracings during labour in 34 cases (36.4%). A further 5 cases were not monitored with CTG during labour for various reasons (mostly lack of sufficient monitors). The most common modifiable factors in CTG interpretation are summarised in Table 1, and examples are given in Figs 4 - 6.

For 22 patients, there was a combination of these two factors: firstly, a lack of recognition of fetal distress, and then a delay getting the patient to theatre once the urgency to deliver was confirmed.

Injudicious use of oxytocin was identified in 16 cases. Many of these were associated with fetal distress, and therefore described above, but a short summary is given in Table 2.

Inadequate clinical assessments, inappropriate management of conditions such as the hypertensive disease spectrum



	Forceps	Elective CD	Vacuum	Vaginal delivery	Emergency CD
n	1	3	19	37	58
%	0.8	2.5	16.1	31.4	49.2

Fig. 1. Method of delivery in study population (N=118). (CD = caesarean delivery.)

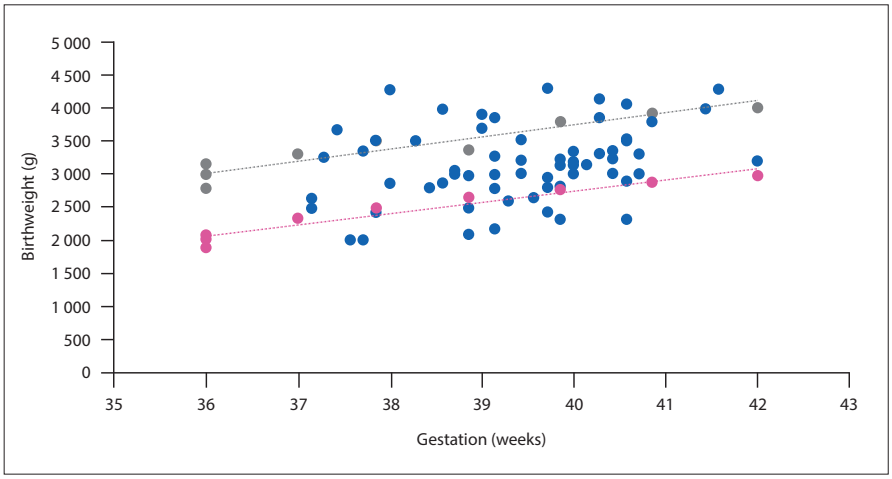


Fig. 2. Birthweight and gestational age. The blue dots represent individual weights of participants. The 10th and 90th centiles are indicated by the pink and grey lines, respectively, using local Tygerberg centiles.[12]

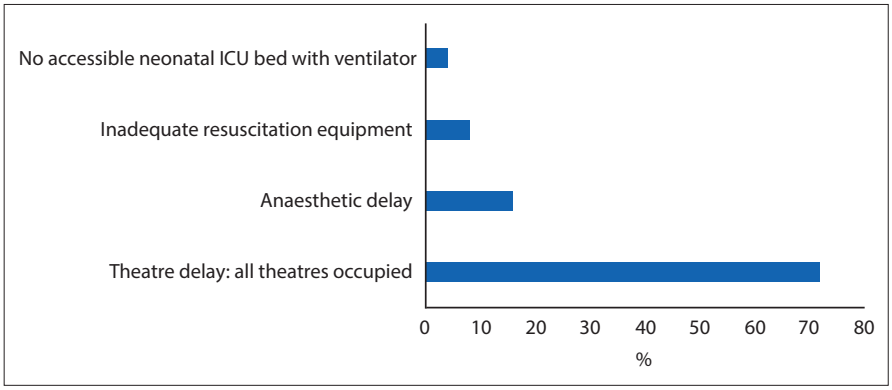


Fig 3. System-modifiable factors (expressed as a percentage of all system-modifiable factors). (ICU = intensive care unit.)

Table 1. Summary of most common modifiable factors related to cardiotocograph (CTG) interpretation

Event(s) not recognised
Sudden fetal bradycardia (lasting several minutes) while on oxytocin infusion, with complete recovery in between. Interpreted as 'patient restless' or loss of contact.
Progressive loss of variability; repeated decelerations interpreted as accelerations (due to baseline shift). (See Fig. 4 for example).
Maternal heart rate traced on CTG (not recognised and interpreted as normal CTG). (See Fig. 5 for example).
Uterine hyperstimulation on oxytocin (tachysystole with decelerations) but oxytocin infusion continued. (See Fig. 6 for example).
Uterine hypertonus (contractions lasting >2 mins while on oxytocin infusion) missed.
Slow but progressive increase in fetal baseline heart rate (up to 170 bpm) missed while on oxytocin.
Slow and subtle progression over several hours from normal CTG to loss of variability to increase in baseline with decelerations. Clinical outcome was chorioamnionitis with maternal and fetal infection.

Table 2. Summary of the most common modifiable factors related to oxytocin usage

Oxytocin not stopped when tachysytole with fetal distress (hyperstimulation) present.
Augmentation of labour done without CTG monitoring.
Oxytocin commenced or continued when external CTG tracing not readable.
Intrapartum resuscitation not done after stopping oxytocin for fetal distress.
Oxytocin restarted several times without clear endpoint for delivery or alternative plan made.

CTG = cardiotocograph.

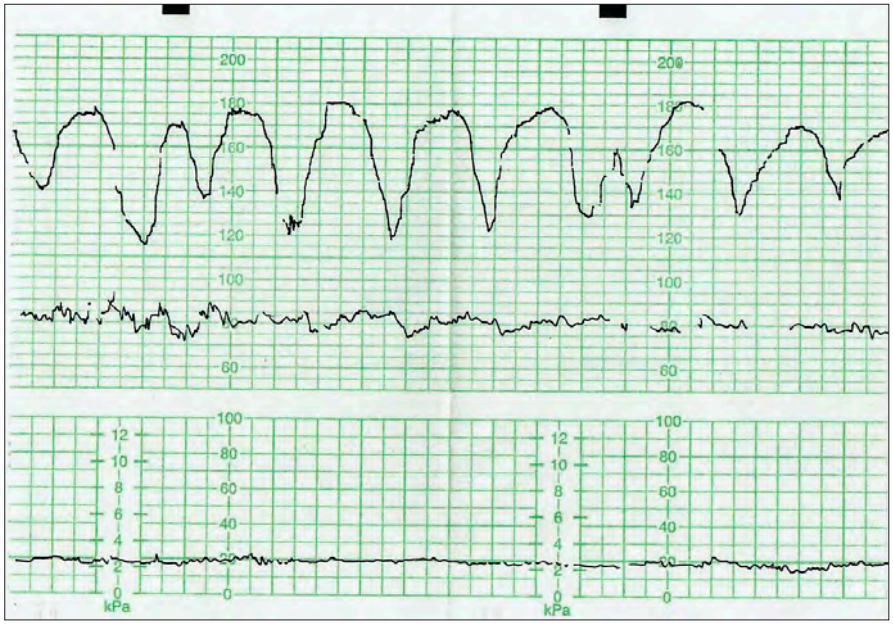


Fig. 4. Example of repeated decelerations misinterpreted as accelerations. Note the complete absence of variability.

in pregnancy, and inaccurate estimation of fetal size were found in 10 (8.9%) cases.

Prolonged labour was also missed in 10 (8.9%) cases. The partogram was either used incorrectly or, when used, was interpreted incorrectly, in 6 cases (5.4%).

Baby outcome

The long-term neurological findings of the babies will be reported separately, but all infants were tracked for a minimum of 2 years after birth as an indication of outcome. The mean hospital stay for all babies was 13 days, with a range of 3 - 103 days. Thirteen babies died during the neonatal period. Of the remaining 105 babies, 11 were lost to follow-up (no evidence of any contact with Western Cape provincial health services anywhere in the province after discharge). The remaining 94 all had follow-up visits at TBH (n=91) or other provincial hospitals (n=3). For the total group, the follow-up visits can be traced for a mean of 80 weeks (3 - 236 weeks). For 25 babies there were continued visits or admissions to TBH >2 years after discharge. The mean number of contacts with healthcare after discharge was 10. The diversity of disciplines visited (including speech therapy, neurology, neurosurgery, cardiology, imaging, respiratory clinics, dietetics, ear, nose and throat and emergency services) is an indication of the impact on health services. The highest number of visits recorded was 111 over 4 years, for 1 of the first babies entered into the audit.

Discussion

This study investigated modifiable obstetric factors in high-risk pregnancies delivering in a large central hospital in SA, where the outcome was moderate to severe NE. Most babies were appropriately grown, but 22% were above the 90th centile for gestation, confirming the high-risk nature of the pregnancies (many women with high BMI or gestational diabetes). The hospital HIE incidence of 5.5/1 000 live births is understandably higher than the 2.3 - 4.3/1 000 reported in community settings in SA.[14]

In 19 cases, a sentinel event occurred that was unavoidable. However, for a number of women and babies there was a double insult: a delay in recognising abnormal fetal heart rate tracings and then a further delay (average of 100 minutes) from booking an emergency CD to incision in the skin. This delay was mostly due to another case already occupying theatre (there is only one emergency CD theatre available 24 hours per day). Decision-to-incision time was utilised as a marker for theatre delay in this audit as the alternative measure, incision-to-delivery time, is influenced by factors that will not necessarily be deemed an avoidable factor for HIE, for example BMI, repeat v. primary CD, skill of surgeon and indication for surgery.[15]

Where there is an immediate threat of life to the baby, the ideal decision-to-incision time for an emergency CD is 30 minutes. This is the target used at TBH and therefore for this audit. This target, however, is not often met, even in high-income countries.[13] The NICE guideline on CD urges a category 1 CD (immediate threat to the baby) to be done 'as quickly as possible', and for fetal compromise that is not life-threatening to be done within 75 minutes.[16] Almost half

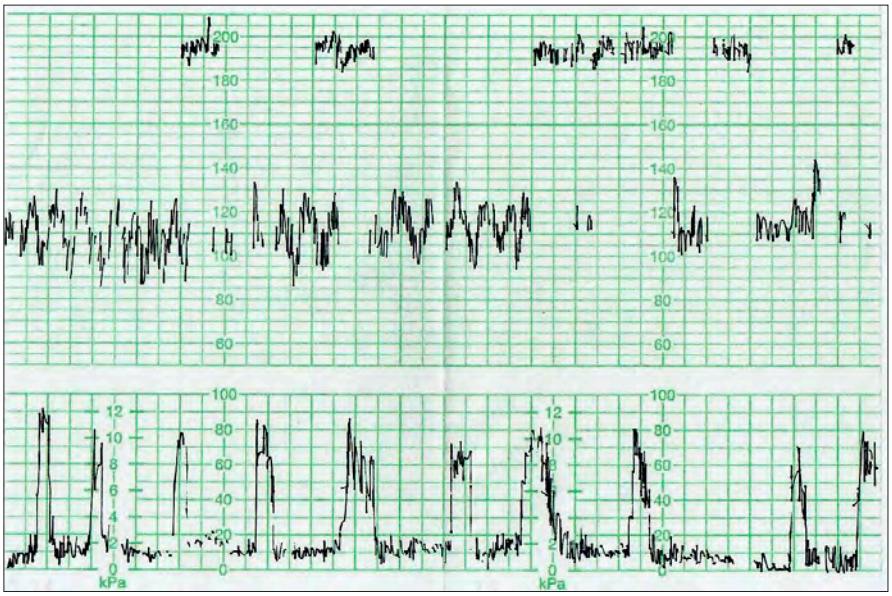


Fig. 5. Maternal baseline heart rate of 120 bpm detected by cardiotocograph machine and interpreted as a 'normal' fetal heart-rate tracing. Intermittent tracing of the actual fetal heart rate (tachycardia >190 bpm) can be seen.

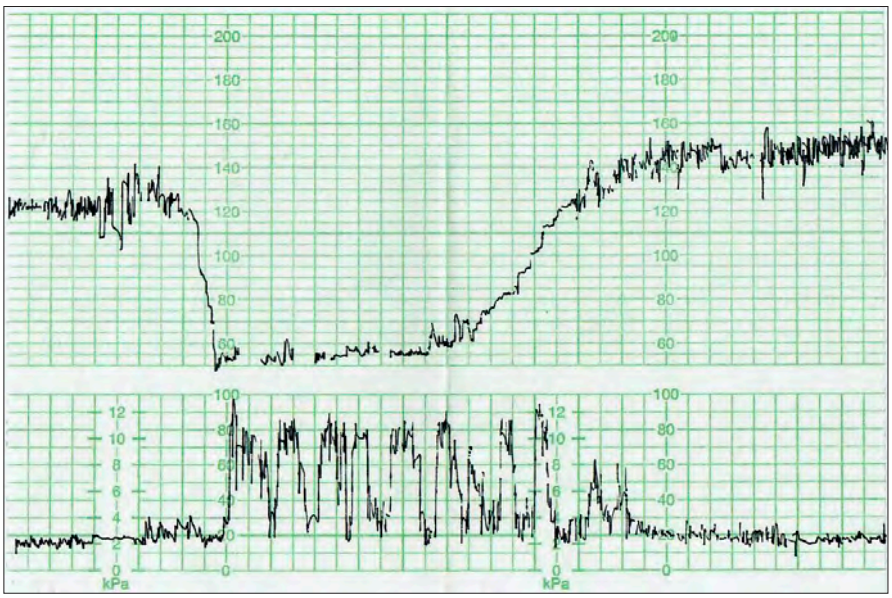


Fig. 6. Uterine hyperstimulation (>5 contractions per 10 minutes with prolonged fetal bradycardia).

(42%) of the vacuum-assisted deliveries were done for fetal distress where an abdominal delivery was the first choice but no theatre was immediately available.

The central question is why fetal distress was not recognised or managed appropriately in cases where an earlier delivery may potentially have changed the outcome for the baby. TBH has 142 maternity beds in total, of which 34 are in the emergency centre. Since 2012, many quality-improvement measures have been put in place at TBH to decrease morbidity, including a larger consultant presence in the labour ward, reorganisation of working hours and a centralised CTG storing and monitoring system.[17] At night and after hours, when most of the avoidable factors occur, there is one registrar and two medical officers available in the emergency centre (another registrar runs the critical care unit). One doctor continuously runs the theatre, and the remaining two doctors manage all the emergency cases. If one considers ideal circumstances, where a doctor can complete a patient assessment every 15 minutes, the number of patients in the emergency centre would make the next review of that patient only possible ~3 hours later. This situation is not unique to TBH but rather indicative of the critical shortage of doctors in SA, and especially in maternity services.[18] The responsibility for intrapartum care is shared with midwives. Nursing staff who are maternity-trained are in equally short supply in SA.[19]

Similar audits elsewhere in the country have identified the same challenges: ambulance delay (not counted in this audit of in-born babies only), lack of access to theatre and lack of recognition of fetal distress. In an audit of HIE from Mowbray Maternity Hospital in Cape Town, 34% of cases had fetal distress not recognised on CTG.[20]

The second question, central to the high rate of litigation in SA for neurological events following birth trauma,[21] is why babies are still born with hypoxic brain damage despite newer technologies and numerous quality-improvement interventions over the years.[22] Gregerson *et al*.[23] in 1999 and Buchmann[24] in 2002 alerted the country to the unacceptably high rates of birth asphyxia and NE. For many hospitals, the number of births have increased over the past 20 years without a concomitant increase in infrastructure and staff numbers. Overcrowding in nurseries (in addition to the risk of infectious outbreaks) leads to delay in admission of sick neonates, creating further bottlenecks in an equally overcrowded labour ward.[25]

The injudicious use of oxytocin was a potential important contributor in many of these cases. The SA maternity care guideline follows the RCOG protocol for oxytocin use, starting at a low dose of 2 mU/min, gradually increasing to a high dose of 30 mU/min, which is higher than the maximum (20 mU/min) allowed at TBH. It is worth pointing out that the physiological dose of oxytocin is equivalent to 4 -6 mU/min, and that doses >16 mU/min do not decrease the CD rate, but can increase the rate of uterine hyperstimulation.[26] Cluver and Odendaal[27] summarise the evidence and dangers of the use of oxytocin in SA.

The strength of this specific audit is that it focuses on inpatient management of complicated pregnancies at the highest level of care available in the state sector in SA. Though not an inherent weakness of the audit, it is noteworthy that many of these women had multiple risk factors, and it would be simplistic to suggest that altering one factor alone would necessarily have resulted in a perfectly normal outcome. High-risk pregnancies preferably need 24-hour specialist-rendered care and one-on-one nursing (the so-called labourist model of obstetric care),[28] an ideal that is difficult to meet even in high-income countries, and certainly unattainable in current SA. The importance of training

medical and nursing staff in CTG interpretation, the correct use and interpretation of the partogram and the judicious use of oxytocin in labour cannot be overstated.

Conclusion

Babies born with severe NE represent a catastrophe firstly for the parents, but also have a major impact on medical staff, resources and morale. Careful intrapartum care can potentially reduce some of the risks. Protocols for the use and monitoring of women on oxytocin should be in place in all hospitals in SA. Immediate access to emergency theatres for labour wards, and appropriately trained healthcare workers, should be priorities for healthcare planners.

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Primary hyperoxaluria: The Baragwanath experience

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Background. Primary hyperoxaluria (PH) is a rare autosomal recessive condition characterised by defects in the metabolism of glyoxylate which leads to excess oxalate production. It is an important disease to diagnose as it can progress to kidney failure (KF).
Objective. To describe the characteristics, diagnosis and management of PH in South Africa and to identify any determinants of KF and death.
Method. A retrospective study of all children younger than 16 years of age, diagnosed with PH at the Paediatric Renal Unit, Chris Hani Baragwanath Academic Hospital, from 1984 - 2017.
Results. A total of 24 patients were identified, of which 20 records were available for complete analysis. The median age of presentation was 6.0 years. The common clinical presentations were urolithiasis (90%), KF (85%), nephrocalcinosis (75%), urinary tract infections (55%) and haematuria (30%). Nephrocalcinosis was better detected on abdominal radiograph compared with ultrasonography. Both nephrocalcinosis (p=0.009) and haematuria (p=0.018) were significantly associated with KF. Five patients had *A112D* genetic mutation in the *AGXT*. Fourteen received dialysis and four were transplanted. The mortality rate in this study was 58.3%.
Conclusion. Clinicians should have a high index of suspicion for PH in patients presenting with haematuria, urolithiasis and KF. This study supports the measurement of urine oxalate levels and abdominal radiographs in screening for PH in children presenting in KF.

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Primary hyperoxaluria (PH) is a rare autosomal recessive condition characterised by defects in the metabolism of glyoxylate which leads to an increased oxalate production and deposition.[1] The most common and severe form is type 1 PH (PH1), due to a genetic mutation in the enzyme, alanine-glyoxylate aminotransferase (AGT) found in the liver peroxisomes.[1] PH1 rapidly progresses to kidney failure (KF), which includes the more severe presentation of infantile PH subtype.[2] The exact prevalence and incidence of PH is unknown.[1]

The age of presentation can range from birth to the sixth decade of life.[1] The most common presentations are urolithiasis, with or without nephrocalcinosis, urinary tract infections (UTIs), haematuria and KF.[3-6] Systemic oxalosis is a result of the deposition of insoluble calcium oxalate crystals in any organ, which usually develops once the glomerular filtration rate (GFR) falls below 40 mL/min/1.73 m^2.[7] The diagnostic work-up includes a 24-hour urine or spot urine analysis for oxalate crystals, genetic mutation analysis, imaging and histology.[1,7] Management of PH includes high fluid intake of 2 - 3 L/m^2 of body surface area per day, alkalinisation of the urine and pyridoxine supplementation.[1,7] Combined peritoneal (PD) and haemodialysis (HD) is also required for the management of PH, but the definitive treatment for PH1 is a combined liver and kidney transplant.[1]

Although primary hyperoxaluria is a rare genetic disorder, the clinical data on PH has been well documented in developed countries.[3,8,9] There are data emerging from developing countries with cohorts of 18 patients from Oman,[10] 26 from Egypt,[6] 44 from Tunisia,[5] and 70 from Jordan.[4] However, no studies have yet been published in sub-Saharan Africa, including South Africa (SA). This study aimed to describe the presentation, diagnosis and treatment of PH at Chris Hani Baragwanath Academic Hospital (CHBAH) in SA, and to identify any determinants of KF and death.

Method

The study population was selected from the Paediatric Renal Unit at Chris Hani Baragwanath Academic Hospital (CHBAH), which is a tertiary academic hospital in Gauteng affiliated to the University of the Witwatersrand. This unit serves the population of Soweto but also receives patients referred from other provinces, as well as, neighbouring countries of SA.

This was a retrospective descriptive study spanning 33 years, 1 January 1984 - 31 December 2017, of all patients younger than 16 years of age and diagnosed with PH. The diagnosis of PH was made if any one of the following was fulfilled: high urine oxalate levels in 24-hour urine collection (>0.7 mmol/1.73 m^2)[1] or spot urine analysis in keeping with hyperoxaluria[1] or birefringent oxalate crystals on histology or genetic confirmation.

Demographics, diagnostic tests, management and outcome data were obtained from the records and further analysed for any association with KF and death. For the definition of the different

variables, please refer to the supplementary file (url:XX).

The categorical data were presented as frequencies and percentages and continuous data as medians with inter-quartile ranges (IQRs). A Pearson's chi-squared test or Fisher's exact test was used to analyse categorical variables for association with KF and death. For continuous variables that was not normally distributed, a Mann-Whitney *U* test was used. The data were analysed at the 95% confidence interval (CI) and *p*-value <0.05 was considered significant. The software used was STATISTICA version 13.3 (TIBCO Software Inc., USA). Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M170423) as well as the medical advisory committee at CHBAH. Approval was also granted by the head of the renal unit to utilise the records.

Table 1. Demographics of the patients with primary hyperoxaluria

	n (%)*	Range
Age		
At first symptom (months), (*N*=20), median (IQR)	67.5 (38.8 - 93.6)	6.0 - 156.0
At hospital presentation (months), (*N*=23), median (IQR)	72.0 (44.0 - 108.0)	7.0 - 156.0
Sex (*N*=24)		
Male	14 (58.3)	
Female	10 (41.7)	
South African (*N*=19)		
Gauteng	11 (57.9)	
Northwest	7 (36.8)	
Free State	1 (5.3)	
Outside of South Africa (*N*=1)		
Swaziland	1 (100)	
Gauteng (*N*=11)		
Soweto	2 (18.2)	
Outside of Soweto	9 (81.8)	

*Unless otherwise specified.
IQR = interquartile range.

Table 2. Clinical presentation of the patients with primary hyperoxaluria, *N*=20

	n (%)
Urolithiasis	18 (90.0)
KF	17 (85.0)
Nephrocalcinosis (by radiographs)	15 (75.0)
UTI	11 (55.0)
Haematuria	6 (30.0)

KF = Kidney failure; UTI = Urinary Tract Infection.

Results

A total of 24 patients were identified with PH, of which 20 records were available for complete analysis. The data available for the four incomplete records were included in the analysis.

Demographics

The median (IQR) age of presentation was 72.0 (44.0 - 108.0) months (Table 1). Nineteen patients (95.0%) were South African, and of African descent, while one was from Swaziland, of British and caucasian descent. Of the 11 patients from Gauteng, 81.8% were from outside Soweto. There was no history of consanguinity or previous family history of kidney disease.

As seen in Table 2, the most common clinical presentation was urolithiasis (90.0%) and KF (85.0%). The median (IQR) estimated GFR ($eGFR_{cr}$) was 6.1 (4.2 - 9.0) ml/min/1.73 m^2. One patient had stage four (CKD) and two patients had normal kidney functions. Figure 1 depicts nephrocalcinosis and urolithiasis detected by plain abdominal radiograph. Most of the patients had more than one test performed for the diagnosis of PH. The median (IQR) 24-hour urine oxalate excretion was 1.4 (0.8 - 2.0 mmol/1.7 m^2/day and 323.6 (232.5 - 594.1) µmol/mmol for spot urine oxalate to creatinine ratio. More spot urine samples were collected compared with 24-hour urine oxalate samples. However, the positivity rate was higher with 24-hour urine collections (87.5%) compared with the spot urine samples (76.9%). Bone marrow aspirate and trephine (BMAT) was performed on 16 patients, of which five (31.3%) had confirmed oxalate crystals under polarised light. Kidney biopsy was done on 11 of the patients, including one postmortem biopsy, and all confirmed oxalate crystals under polarised light.

Echocardiography was done on 15 patients, eight (53.3%) of which had normal findings and seven (46.7%) had abnormal findings: two patients (13.3%) had left ventricular hypertrophy, two patients (13.3%) had small pericardial effusions (range 4 – 8 mm), one patient (6.7%) had diastolic dysfunction, and one patient (6.7%) had a patent ductus arteriosus (PDA). Lastly, echo-bright myocardium was observed in one patient (6.7%), but no speckling was observed. There were seven electrocardiograms (ECG) available for analysis, four were normal but three patients had prolonged, corrected QT intervals. Of the three patients, two had documented hypocalcaemia.

Genetic studies were done on six patients, and all had confirmed type 1 PH. Five of the patients were homozygous for *A112D* mutation and the other had a heterozygous mutation for two different alleles, *c335C*>A (*p.A112D*) and *c.473C*>T (*p.S158L).*

On initial presentation, 15 (75.0%) patients had nephrocalcinosis on abdominal radiograph. Of the remaining five, one had urolithiasis without nephrocalcinosis; two were not available and two of the patients, who had normal kidney function, showed normal plain abdominal radiographs. This contrasts with the 17 ultrasounds that were performed, where only five (29.4%) ultrasounds confirmed the presence of medullary or cortical nephrocalcinosis. Of the remaining 12 ultrasounds, five reported hyperechoic kidneys and the remaining seven sonars did not identify nephrocalcinosis. Nephrocalcinosis was significantly associated with KF (*p*=0.009).

Management

Routine management included alkalinisation of urine, high fluid intake and pyridoxine. The median (IQR) dose of pyridoxine was 6 (5 – 10) mg/kg/dose. Response to pyridoxine treatment was not assessed in this study. A gastrostomy tube was inserted for a 7-month-old infant to ensure adequate fluid and protein intake. Three patients had endoscopic lithotripsy by the urologist prior to referral to the renal unit.

A total of 14 patients received dialysis and four patients died prior to the initiation of dialysis. Of the 11 patients that were referred

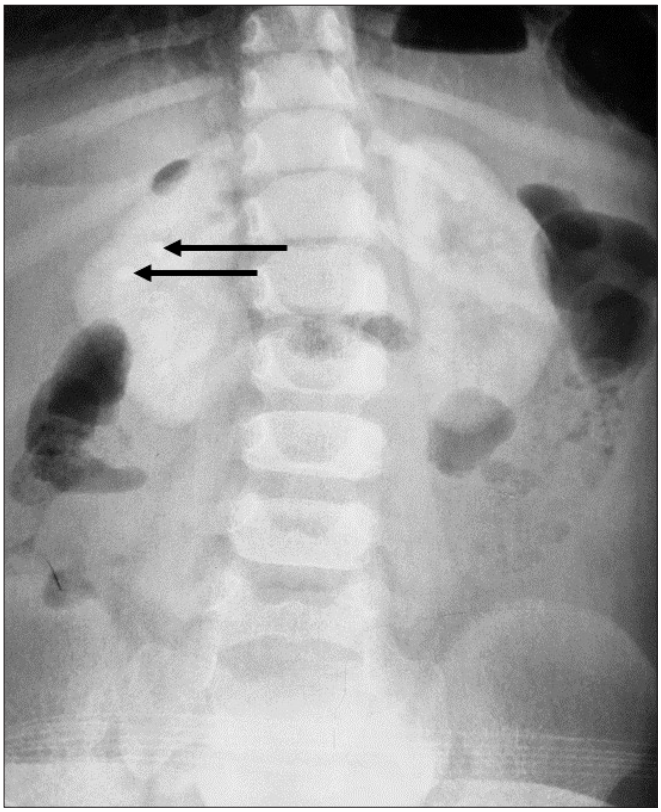

Fig. 1. Abdominal x-ray with primary hyperoxaluria showing nephrocalcinosis, as delineated by the radio-opacities outlining both kidneys, and urolithiasis as indicated by the arrows

for transplantation, four had been transplanted, of which two received combined liver-kidney transplantation and the other two had kidney transplantation. Of the remaining seven patients, two were waiting to be listed, four patients demised prior to transplantation, and one was lost to follow-up. In this study, 14 of the 24 patients demised resulting in a mortality rate of 58.3%.

There were significant associations between the following factors with KF: nephrocalcinosis (p=0.009), and haematuria (p=0.018). However, no significant determinants of death were identified.

Discussion

This is one of the first studies reporting on PH in SA. It highlighted the important differences in the presentation of patients in this cohort compared with other countries, such as North Africa and the Middle East. The most notable difference was the age of presentation. There was no history of consanguinity in this study, compared with the North African[5] and Middle Eastern cohorts.[4,6,10] The high prevalence of PH seen in the North African and Middle Eastern countries may be due to the high rates of consanguinity.[1]

In this study, the median age of onset of first symptoms was 67.5 months (5.6 years), which is comparable with the Dutch cohort (median age of 6.0 years).[9] The median age of presentation was 72 months (6 years) which is much older compared to the Egyptian cohort of 3 years of age.[6] The difference in age of presentation was a result of the higher proportion of infantile PH (35.3%) in the Egyptian cohort[6] compared with this study cohort of 4.2%.

The most common clinical presentation in this study was urolithiasis, KF and nephrocalcinosis, which was similar to the other international cohorts.[3,6,9,10] In this cohort, nephrocalcinosis was identified more often on plain abdominal radiographs compared with ultrasound, and as reported in other studies.[11,12]

It has been shown in a few studies that cortical nephrocalcinosis is associated with rapid progression to KF.[5,6,8,9,13] In this cohort, the presence of nephrocalcinosis was associated with KF (p=0.009). The poor recognition of nephrocalcinosis on sonography may be due to the low diagnostic yield and the high inter-observer variability in this imaging modality.[14] In addition, the hyperechoic renal parenchyma on ultrasound could represent nephrocalcinosis, but not interpreted as such. This highlights the importance of plain abdominal radiographs, as well as the utilisation of more than one imaging modalities to improve nephrocalcinosis-diagnosis in PH.

The percentage of positive results were higher in the 24-hour urine collections (87.5%) compared with the spot urine samples (76.9%). A 24-hour urine collection is the gold standard diagnostic test and is preferred over a spot urine sample, as it is more sensitive and specific.[15] However, a 24-hour urine collection is technically more challenging, and requires accurate timing and collection of all urine passed during that time period.[16] A spot urine oxalate creatinine is also more practical in younger children.[15]

The decline in GFR typically results in reduction in urine oxalate excretion.[16] However, this was not evident in this study. Urinary oxalate levels were diagnostic in 11 patients with $eGFR_{cr}$ < 30 mL/min/1.73 m^2, and remains an important diagnostic tool for PH even in advanced stages of CKD. Haematuria was shown to be significantly associated with KF (p=0.018), showing the importance of routine urine dipsticks.

Genetic testing was performed on six of the patients, of which five had homozygous *A112D* mutation (type 1 PH). This mutation was previously identified in two unrelated patients, one from Botswana and one South African.[17] *A112D* is most likely a common mutation in the Southern African population as previously suggested.[17] One patient was heterozygous for two different alleles, *c335C*>A (*p.A112D*) and *c.473C*>T (*p.S158L*).

Given the small sample size there was no significant association noted between the genetic mutations with KF (p=1.0). Interestingly, of all the genetically-confirmed PH1 patients, four had KF while one had normal kidney function. The patient with the normal kidney function and type 1 PH likely had a slow progression of the disease, supporting the notion that simply having the genotype does not necessarily translate into full phenotypic expression. Further studies would need to be done to identify phenotypic correlation to homozygous *A112D* mutation. It was not possible to determine the PH subtypes of the remaining 11 patients, who had presented with KF, without genetic analysis.

Histology remains an important tool in the diagnosis of PH, particularly in anuric patients where measuring urine oxalate levels is not possible. Kidney biopsy appeared to be more relaible than BMAT in this cohort. There was no significant association between systemic oxalosis and KF, or death.

The cardiac abnormalities noted in the study population, including left ventricular hypertrophy and diastolic dysfunction, could be related to the hypertension seen in chronic kidney disease, but it could also be attributed to oxalate deposition as observed in another study.[18] Increased cardiac echogenicity has also been described in patients with PH as a result of deposition of oxalate crystals,[19] which was observed in one study patient.

There was one study patient that had a prolonged QT interval with normal calcium levels. This could be a result of oxalate deposition as arrhythmias have been described in PH patients.[18] There was no significant association between the cardiac manifestations and KF, or death. Non-invasive screening for cardiac involvement

in all patients with PH is recommended. Larger studies would be valuable in characterizing the cardiac manifestations of PH.

A large proportion of the study population were referred from the North West (36.8%) and of those that were from Gauteng, 81.8% were from outside of Soweto, the drainage area for CHBAH. Transportation costs incurred by patients may account for as much as 27.1% of the average family income.[20] In addition to the transportation costs, the need for families to relocate to access dialysis and further treatment also results in high social strain and disruption to the family unit, as well as, daily life.

It is possible that the mortality rate in this study was higher than 58.3%, as three of the four patients that defaulted follow-up had $eGFR_{cr}$ <15 mL/min/1.73 m^2. This mortality was higher compared to the Egyptian cohort of 42.3%, of which 65.4% of the patients had KF.[6] The higher mortality rate in this study was likely due to late presentation, as well as, the higher portion of KF (85.0%) in this cohort.

This retrospective study was limited by the small sample size, the lack of availability and incompleteness of the records in four children. In this cohort, the lack of significance between systemic oxalosis with KF or death and the determinants of death, was likely due to the small sample size. Logistic models for analysis of the determinants of KF and death could not be done due to the small sample size. There is a referral bias given that only patients that were referred to the renal unit were included. The milder and more severe types of PH may be missed, as the former may be asymptomatic, and the latter die before referral or presentation. Despite these limitations, this study is the first in SA to document PH in children, and future studies may add to the genetic data.

Conclusion

Clinicians should have a high index of suspicion for PH in patients presenting with haematuria, urolithiasis and KF. This study supports the measurement of urine oxalate levels and abdominal radiographs in screening for PH in children presenting in KF.

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Infant injuries treated at Red Cross War Memorial Children's Hospital, Cape Town, South Africa

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Background. Infants are entirely dependent on their caregivers, especially <6 months old when they are not yet mobile. While the epidemiology of injury among children in general has been described, the exact causes of infant injury have never been investigated in South Africa (SA).
Objective. To describe causes of injury in infants aged <12 months, stratified for the four quarters of the first year of life, in order to identify opportunities for targeted prevention strategies based on local data.
Methods. This retrospective audit study used data collected by ChildSafe SA from the Red Cross War Memorial Children's Hospital in Cape Town, SA, over a 4-year period from January 2013 to December 2016. Infants <1 year of age presenting to the hospital's trauma casualty department were included. Additionally, mortuary data on traumatic infant deaths in the hospital's catchment area were collected.
Results. A total of 2 279 injured infants were identified. More than half were male (55%; *n*=1 250) and the median age was 8 months (interquartile range 5 - 10 months). Leading causes of injury were falls (42%; *n*=957) and burns (32%; *n*=736). A significant association between the age group and the cause of injury ($p<0.001$) was found. From 2014 to 2016, an additional 27 infants were traumatically injured and died before arriving at the hospital.
Conclusion. Falls and burns are a significant contributor to the burden of infant injuries in Cape Town. This underlines the urgent need for targeted prevention strategies to improve safety, taking poverty into account.

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Trauma injury has a great impact on people's health, but children up to the age of 1 year are especially vulnerable[1,2] owing to their immature anatomy, skeletal composition, cardiovascular performance and drug metabolism. Falls – from a bed, couch, baby equipment or the arms of a caregiver – are the leading cause of injury in children <1 year old.[3,4] Burns are a second major cause of injury in infants. In Africa, the annual incidence of fire-related burns in children <1 year old is 35 per 100 000. This is more than three times the world average for this age group. Other known causes of injury in infants are interpersonal violence/assault, traffic crashes, poisonings and choking.[5-7] Most injuries occur at home, often as a consequence of household hazards such as loose hanging kettle cables and beds without safety bars, lack of supervision, as well as the increased mobility of older infants.[4,7,8]

Infants <6 months old are largely pre-mobile and dependent on their caregivers. When aged 6 - 12 months, they develop the ability to crawl, roll and eventually walk, and are then at greater risk for injury. Even though injuries in children <1 year old account for only 2% of all injuries in children in low- and middle-income countries (LMICs), unintentional injury death rates in this age category are highest when compared with the older age groups.[2,3] The infant death rate from burns is highest in LMICs: 11 per 100 000 population.[3] Standard age groupings for paediatric injury research have been developed.[3,9] In most studies, however, children <12 months of age are taken as one group. Unfortunately, this practice may mask age-related injury trends in infants.

While the epidemiology of injury among children in general has been described, causes of infant injury have never been validly investigated in South Africa (SA). Insight into the leading causes of injury specified for different stages of the first year of life can help to develop interventions to prevent injury.[6,10] This study aims to describe causes of injury in children <12 months admitted to the trauma casualty department of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, SA, stratified for different age groups.

Methods

Study design

This is a retrospective, descriptive audit study.

Patients and setting

ChildSafe SA is an independent non-governmental organisation, established in 1978 (www.childsafe.org.za). Since 1991, ChildSafe SA has systematically kept a computerised childhood trauma surveillance system of all injured children presenting to the RCWMCH trauma unit, which serves as a national information system for childhood injuries in SA. Funding is provided by numerous donors.

We analysed available data of children <1 year old (365 days) seen between January 2013 and December 2016. Ethical approval was obtained from the Human Research Ethics Committee, University of Cape Town Faculty of Health Sciences (ref. no. 239/2018). No recruitment or informed consent was necessary as this is a retrospective study.

Data collection

ChildSafe has developed a data collection form that consists of six major domains: (*i*) patient demographics; (*ii*) cause of injury; (*iii*) place of occurrence; (*iv*) severity of injury; (*v*) suspicion of abuse;

and (*vi*) discharge destination. This ChildSafe form is completed by the attending physician for every child presenting at the trauma casualty department of the RCWMCH. The causes of injury are classified as assault, birth injury, bites, burns, caught [between objects], falls, foreign bodies, pulled up/lifted, struck, transport, miscellaneous or unknown. We translated the different causes of injury into ICD-10-CM codes for external causes of morbidity and mortality according to the International Classification of Disease. The ICD-10-CM codes classified under the main causes of injury are shown in Table 1. The place of occurrence contains the following options: own home; road/pavement; other home; public place; school/creche; sport; other; and unknown.

The severity of injury is classified with the use of the RCWMCH's four-point abbreviated injury score (AIS) as 'mild', 'moderate', 'severe' or 'mortal'.[11] Suspicion of abuse is represented by the abuse code on the ChildSafe form, and is classified as 'no abuse', 'possible abuse' or 'abuse'.

All variables were checked for missing or incorrect values in the database. If missing or incorrect values were identified, additional information was obtained from the medical records and processed in the database by the principal investigator (KKS). For the analysis we created four age groups (0 - 2 months old, 3 - 5 months old, 6 - 8 months old and 9 - 11 months old), corresponding with the different levels of child development and mobility.

Mortuary data on traumatic infant deaths (<1 year old) in the hospital's catchment area for the study period were collected from the University of Cape Town Division of Forensic Medicine and Toxicology. This way we additionally included fatal injuries in which the infant did not make it to the hospital. Collected data included cause of injury and manner of death (intentional v. non-intentional) in infants who had died before arrival at the hospital.

Outcomes

The primary outcome is cause of injury. Secondary outcomes are place of occurrence, severity of the injury and the nature of fall injuries and burn injuries.

Data analysis

Normally distributed variables are presented as mean (standard deviation), and non-normally distributed variables as median (interquartile range (IQR)). Descriptive statistics (frequencies and cross-tabulations) were used to characterise injuries by cause for each age group. Age-related injury patterns were compared with published norms for child growth and development. Differences in categorical variables between age groups were tested with χ^2 or Fisher's exact tests, as appropriate. If exact test was not computable, we applied Monte Carlo. A p-value <0.05 was considered statistically significant. All data management was conducted in Excel (Microsoft Corp., USA) and statistical analyses were performed in SPSS for Windows, version 24.0 (IBM SPSS Statistics, USA).

Results

According to the trauma surveillance registry, 2 279 infants <1 year old presented at the RCWMCH's trauma casualty department between January 2013 and December 2016. Table 2 gives the background characteristics of this patient group. More than half were male (55%; *n*=1 250) and the median age was 8 months (IQR 5 - 10).

Most injuries were classified as moderate (51%; *n*=1 170) or minor (47%; *n*=1 084). Burn injuries in particular were frequently classified as moderate (83%; *n*=614). One infant had died at the trauma casualty department and therefore scored 'mortal' on the AIS. This was a 9-month-old female with a gunshot wound in her head.

Causes of injury

Table 3 provides details of the occurrences of the various causes of injury for the total group and the different age groups. Falls were the most frequent cause of injury, comprising 42% (*n*=957) of all injuries. This holds true for the three youngest age categories as well. The proportions of falls in the three youngest age groups were comparable, but in the oldest age group this proportion was lower than that in the three youngest age groups. In the oldest age group, burns were the most common injury (44%). Of all injuries, 70% had occurred in the two oldest age groups (*n*=1 604). A significant association between the age group and the cause of injury (p<0.001) was found, in that assault was more frequent in younger infants. Older infants were more likely to be injured from burns and foreign bodies or caustic ingestion. In the two youngest age groups, the cause of injury was more likely to be unknown than in the two oldest age groups.

Falls

Falls from bed accounted for almost half of the fall injuries (49%; *n*=471). Other common types of fall were falls from attendants' arms (16%; *n*=154), falls from toy devices or playground equipment (8%; *n*=76), falls from stairs (6%; *n*=56) and falls from furniture (4%; *n*=38). The remaining 17% were defined as 'other falls' (*n*=162), consisting of falls while trying to walk or stand, falls out of car seats and unknown mechanisms of falls. Fig. 1 shows the distribution of age groups among the different types of falls. There was a significant association between the type of falls and the age groups (p<0.001), in that infants <6 months were more often dropped out of the attendant's arms, and older infants endured a greater number of other fall types. Of all falls, 22% led to a fracture (*n*=210), and 86% of the falls occurred inside the infant's own home (*n*=823).

Burns

Burn injuries were the second-most common cause of injury in the total group (32%; *n*=736), and were more often seen in male than in female infants (p=0.007). Burn injuries occurred more frequently in the two older age groups (p<0.001): the proportion of burn injuries increased from 10% in the youngest age group to 44% in the oldest age group. Hot water burns contributed to over 80% of all burns (84%; *n*=615). The distribution of age groups among the different types of burns is seen in Fig. 2. Burns were in most cases (95%) sustained at home.

Other injuries

Eighty-four infants were injured due to being struck (4%) (Table 3). Of these 84 cases, 43 (51%) resulted in tissue damage such as abrasions, lacerations and closed tissue injuries.

Of the 73 assaulted infants, 60 (82%) were physically assaulted; 10 (14%) sexually assaulted and 3 (4%) abandoned or neglected. There was a significant association between assault and age group (p<0.001), in that assault was mostly seen in the two youngest age groups. In addition, females were more frequently victims of sexual assault, whereas physical assault was seen more often in males (p=0.019).

Injuries due to foreign bodies or caustic ingestion occurred significantly more often in infants >6 months of age (p<0.001). In the foreign body cases, airway foreign bodies (59%; *n*=43)

Table 1. ICD-10-CM codes per cause of injury

Major category	Specific category	ICD-10-CM codes
Assault	Abandonment/neglect	T74.02, T74.32, T76.02, T76.32, Y06, Y07
	Physical assault	T74.12, T76.12, X91, X95, X97, X99, Y00, Y01, Y04, Y07
	Sexual assault	T74.22, T74.52, T76.22, T76.52, Y05, Y07
Birth injury	-	P10-P15
Bites	Dog bites	W54.0
	Rat bites	W53.11
	Other bites	W55.81, W57
Burns	Flame burns	X00-X09
	Fluid burns	X10, X12, X19
	Hot water burns	X11, X12
	Heat contact	X15, X16
	Other burns	W85, W86, X00.1, X01.1, X02.1, X03.1
Caught between objects	-	W23
Falls	Attendant's arms	W04
	Bed	W06
	Furniture	W07, W08
	Playground equipment	W09
	Stairs or steps	W10.0, W10.1, W10.2, W10.8, W10.9
	Other falls	W17-W19
Foreign body	Airway	T17, T18, W79, W80
	Ingestion	X49, Y19
	Non-airway	W45
Pulled up/lifted	-	Y93.F2
Struck	-	W20-W22
Transport	MVA	V40-V49, V70-V79
	Pedestrian	V01-V06, V09
	Other	V80
Miscellaneous		T59.3, X00.1, X01.1, X02.1, X03.1, X50, Y28, Y29, Y33, Y93.F1, Y93.F9
Unknown	-	Y34

ICD = International Classification of Diseases; MVA = motor vehicle accident.

were more common than non-airway foreign bodies (22%; *n*=16). Ingestion occurred in 13 cases (19%).

The most common transport-related injuries were motor vehicle crashes (72%; *n*=46). Seventeen infants were injured as pedestrians (27%).

In 23 cases (70%) of all infants who were injured by being pulled up or lifted, this resulted in an elbow injury. Dislocations were mostly caused by lifting up an infant (42%; *n*=14).

Being caught between two things was the cause of injury in 31 infants (1%).

Birth was the cause of injury in 30 cases, accounting for 1% of all injuries.

The 32 bites were classified as rat bites (*n*=10; 44%), dog bites (*n*=7; 30%), human bites (*n*=2; 9%) and other bites (*n*=4; 17%).

Cases were grouped under miscellaneous if the injury was caused by a sharp or a blunt object, massage, washing, crawling, pepper spray or smoke inhalation.

Mortuary data

Mortuary data on infants in 2013 were missing. Over the years 2014 - 2016, a total of 27 infants <1 year of age died before arrival in the hospital. Of the deceased infants, 14 (52%) were <6 months and 13 (48%) were >6 months of age. The related causes of injury in these infants were assault (30%; *n*=8), drowning (26%; *n*=7), burns (26%; *n*=7), road traffic accidents (7%; *n*=2), choking (7%; *n*=2) and falls (4%; *n*=1). Eighteen died unintentionally and 9 were murdered. The methods of murder were assault in 8 cases and drowning in 1 infant.

Discussion

The aim of this study was to describe the characteristics of injuries in children <1 year old in Cape Town, SA. We found that most injured infants were >6 months of age. The following may serve as an explanation: with increasing age, the child's mobility gradually advances from being only able to roll over at 4 months, but sit up at 6 months, pull up to a standing position at 9 months and eventually start walking at the age of 12 months.[12]

Previous research into paediatric injuries found that two-thirds of injuries were of minor severity in children aged <13 years.[10] Strikingly, the severity of more than half of the injuries in the present study was classified as moderate. This suggests that infants <1 year of age are more likely to be injured more seriously after experiencing a trauma than children of other ages.

Falls

Between 2013 and 2016, falls were the most frequent cause of injuries in infants presenting to the RCWMCH, and were the leading cause of injury in infants aged ≤9 months. Other research likewise cites falls as the most common cause of paediatric injury.[2,7,13] Owing to infants' rapid growth and developmental changes, the frequency and mechanism of falls change with increasing age. A higher proportion

of children >6 months of age presented to the trauma unit as a result of falls. In previous research, younger children were found to be more likely to be dropped from a caregiver's arms or to fall from furniture.[12] Our findings support this, and suggest that infants <6 months of age are at particular risk of being dropped. Parents should therefore be educated about the fast development of mobility in infants, to create more awareness of the hazards in the infant's first year of life.

It is striking that even though infants <3 months old are usually not able to roll over, almost half of the infants aged 0 - 2 months who had experienced a fall were reported to have fallen out of bed. This raises some serious concerns about the veracity of the history provided, and should be considered a marker for child abuse until proven otherwise. It will help to educate providers that (*i*) inconsistent and developmentally implausible history and (*ii*) injury pattern requiring mobility in a non-mobile child are highly suspicious for child abuse.

In concordance with our study, other research has also indicated that the majority of non-fatal fall injuries occur in the home environment.[10] The significant burden of fall injuries highlights the urgent need for targeted interventions to improve the safety of infants, especially within the home. Mechanisms of falls are highly dependent on context, but in SA there is currently a lack of evidence-based research on risk factors and effective interventions to prevent falls in this specific age group. In the search for effective prevention strategies, poverty should be taken into account, since social class and childhood falls have shown a strong relationship.[3] Not only are not all interventions applicable in poor-quality housing, but also, in poor families, children are more often left unsupervised.[3]

Table 2. Background characteristics of the study population (*N*=2 279)

Characteristic	Frequency	Percentage
Age		
0 - 2 months	317	14
3 - 5 months	358	16
6 - 8 months	690	30
9 - 11 months	914	40
Median (IQR) age, months	8 (5 - 10)	
Sex		
Male	1 250	55
Female	1 029	45
Severity of injury*		
Minor	1 084	47
Moderate	1 170	51
Severe	22	1
Mortal	1	<1
Suspicion of abuse†		
No	2 157	95
Possible	77	3
Yes	35	2
Place of occurrence		
Own home	1 993	87
Road/pavement	61	3
Other home	48	2
Public place	41	2
School/creche	39	2
Sport	3	<1
Other	18	1
Unknown	75	3

IQR = interquartile range; GP = general practitioner; ICU = intensive care unit.
*For 2 patients the severity of injury was not completed on the data collection form.
†For 10 patients the abuse classification was not completed on the data collection form.

Burns

The second leading cause of injury in the present study was burns. We found a predominance of burn injuries in males compared with females. Previous research conducted in SA showed the same predominance,[9] but in the global literature burns occur more often in females. Similarly to the global literature,[3] our study found that most burns had been sustained in the home environment. Flame burns were more frequently seen in the youngest age groups, while hot water burns occurred more frequently in infants >6 months old. Overall, hot water burns accounted for most of the burn injuries in infants. The increased vulnerability for burns with older age can be explained by the fact that when a child is able to stand upright, (s)he can more easily reach for hot objects and loose hanging kettle cables.

Strengths and limitations

A strength of this study is the distinction made between different age groups. Where other research used standard age groupings for paediatric injury, and infants <1 year of age are taken as one group,

Table 3. Distribution of causes of injuries by age

Injury cause	Total (*N*=2 279), *n* (%)	0 - 2 months (*n*=317), *n* (%)	3 - 5 months (*n*=358), *n* (%)	6 - 8 months (*n*=690), *n* (%)	9 - 11 months (*n*=914), *n* (%)
Falls	957 (42)	150 (47)	168 (46)	317 (45)	322 (35)
Burns	736 (32)	32 (10)	66 (18)	235 (34)	403 (44)
Struck	84 (4)	19 (6)	17 (5)	26 (4)	22 (2)
Assault	73 (3)	22 (7)	20 (6)	14 (2)	17 (2)
Foreign bodies	73 (3)	2 (1)	6 (2)	18 (3)	47 (5)
Transport	64 (3)	10 (3)	20 (6)	17 (3)	17 (2)
Pulled up/lifted	33 (2)	6 (2)	8 (2)	11 (2)	8 (1)
Caught	31 (1)	4 (1)	7 (2)	4 (1)	16 (2)
Birth injury	28 (1)	27 (9)	1 (<1)*	0 (0)	0 (0)
Bites	23 (1)	6 (2)	3 (1)	5 (1)	9 (1)
Miscellaneous	42 (2)	10 (3)	7 (2)	10 (1)	15 (2)
Unknown	135 (6)	29 (9)	35 (10)	33 (5)	38 (4)

Fisher's exact test = 347.179; $p<0.001$. The category 'miscellaneous' includes injuries caused by a sharp object, machinery and other injuries.
*Birth injury in older infant was discovered later.

we were able to relate injuries to the level of development. This way we reduced the risk of masking small injury trends. Another strength is the use of mortuary data on traumatic infant deaths, which has increased the accuracy of the results.

A possible limitation of this study is the severity of injury assessment. We have tried to standardise severity assessment through the use of the RCWMCH's AIS,[11] yet the severity of injury might have been subjectively assessed in some cases owing to the time pressure

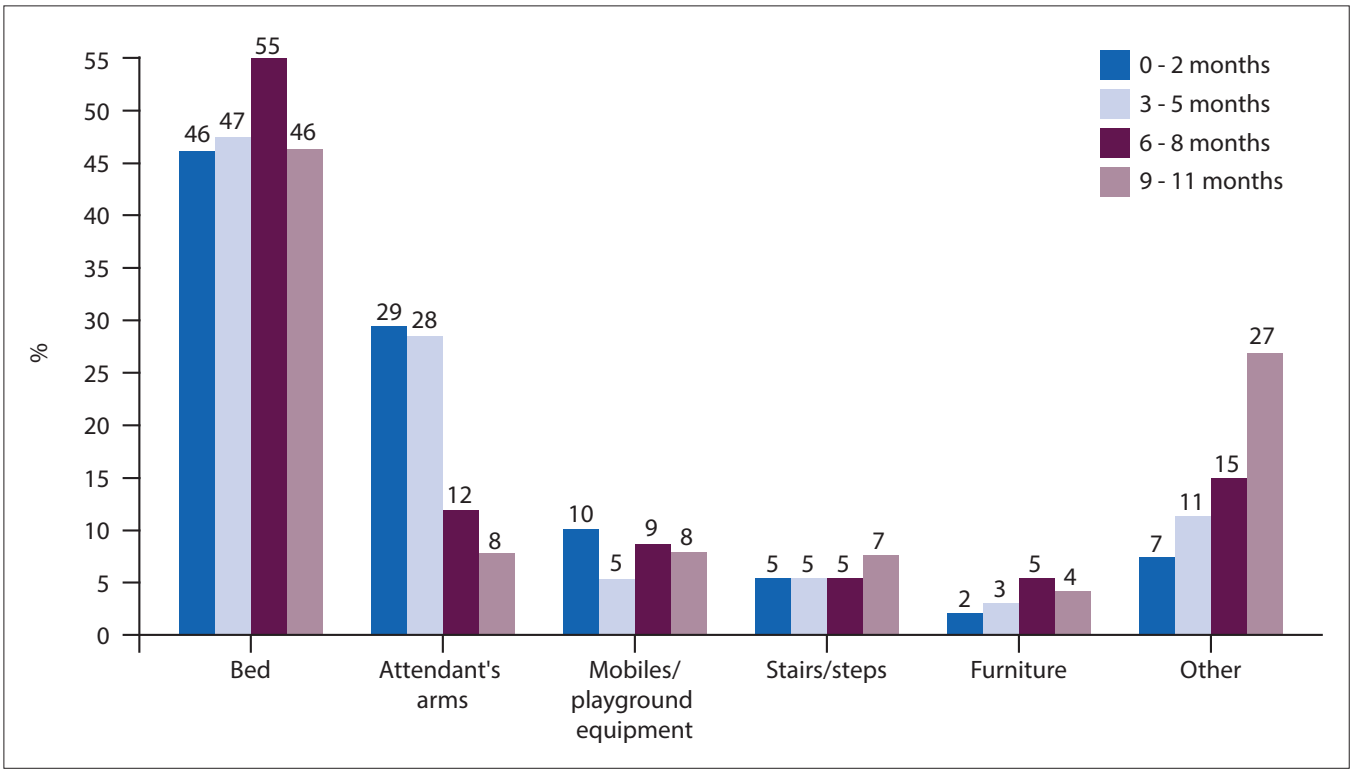

Fig. 1. Nature of fall injuries per age group in percentages (n=957).

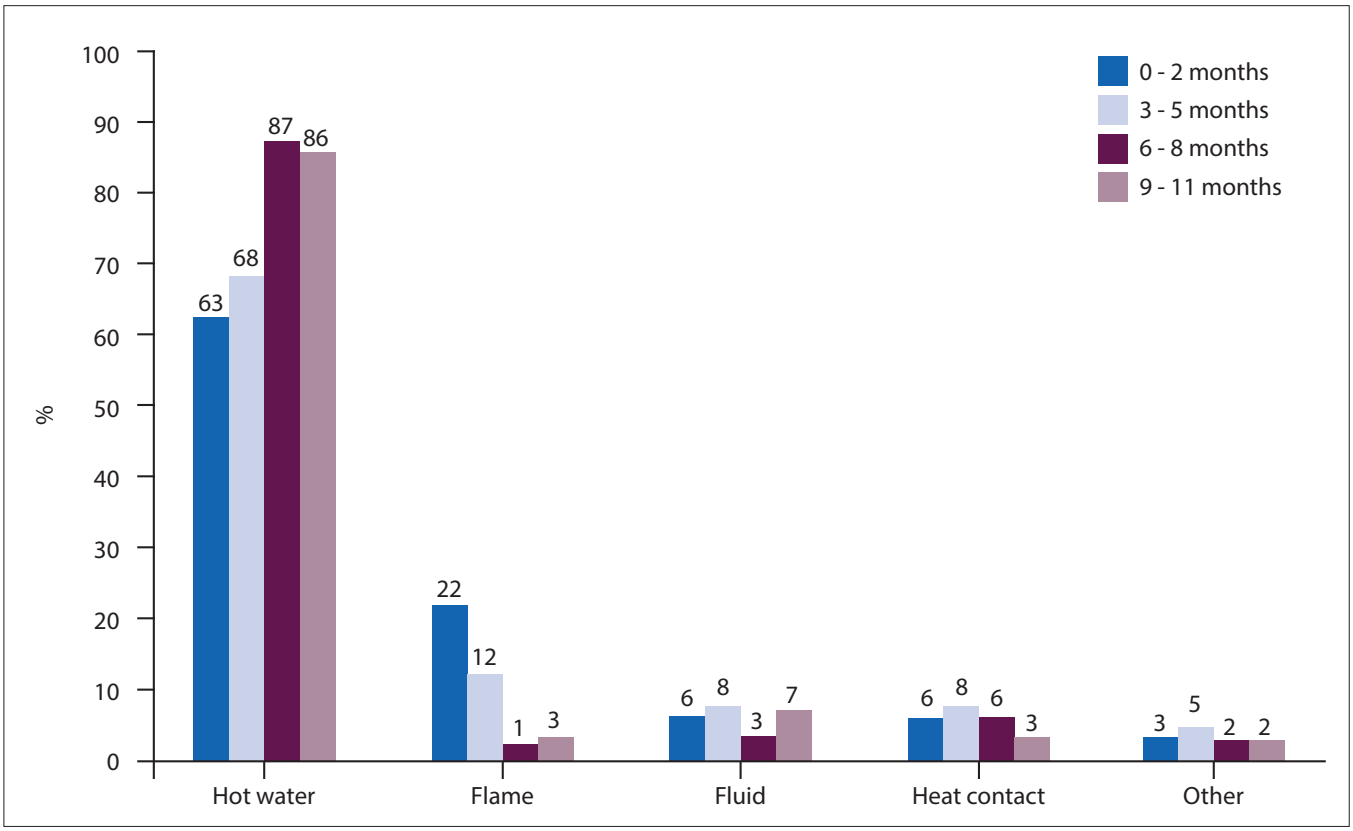

Fig. 2. Nature of burn injuries per age group in percentages (n=736).

associated with high emergency. Also, by using this RCWMCH's modified AIS, this study is limited in comparing the severity of injury with that in studies from other settings.

A further limitation is that RCWMCH's trauma registry does not follow admitted children through the course of their hospitalisation. All data collected pertained to the injured child's stay in the trauma casualty department. Outcome data, including mortality, morbidity and hospital length of stay, were therefore not available.

A final limitation of this study is the lack of information about abuse. The abuse code was collected from the ChildSafe form, which is routinely completed at the moment the child presents to the trauma unit of the RCWMCH. At that point in time, the provision of adequate healthcare is the priority, and signs and signals of abuse may be overlooked at that stage. Besides, the abuse code only indicates whether abuse was suspected at the moment of completing the ChildSafe form, not if abuse was actually confirmed. Therefore, the abuse code does not seem a reliable tool to investigate abuse in infants. Future in-depth research into determinants predicting abuse in infants is necessary.

Conclusion

The most likely causes of injury in infants <1 year of age seen in the trauma casualty department are falls or burns. The significant burden of these injuries emphasises the urgent need for targeted prevention strategies to improve infants' safety, especially within the home. Parents should be educated about the fast development of mobility in infants and the milestones they will reach in their first year of life. Interventions should be devised that take poverty into account. Findings also suggest that abuse is under-recognised: more research into determinants that predict child abuse in a standardised way is necessary. The use of a screening tool at the trauma unit should be considered.

Declaration. This study was completed as part of KKS's MMed, but changes have been made since submission.

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The trajectory of general movements from birth until 12 - 14 weeks corrected age in very low-birthweight and extremely low-birthweight infants born preterm

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Background. General movement assessment (GMA) is an assessment tool with high predictive validity for neurodevelopmental outcomes in preterm infants. Information available describing the trajectory of general movements (GMs) in high-risk preterm-born infants and the use thereof in low- and middle-income countries is limited.
Objective. To describe the trajectories of GMs from birth until 12 - 14 weeks' corrected age, and determine the association of known perinatal risk factors on GM trajectories in very low-birthweight and extremely low-birthweight preterm infants.
Methods. This was a longitudinal, prospective cohort study with 119 preterm infants born at <33 weeks' gestation and with a birthweight <1 500 g. GMs were recorded at four key age periods: 1 - 2 weeks after birth to 33 weeks post menstrual age (PMA); 34 - 37 weeks PMA; term equivalent age (TEA); and 12 - 14 weeks corrected age. Detailed perinatal data were collected.
Results. A total of 300 GMAs were conducted, 157 during the preterm age, 55 during TEA and 88 at 12 - 14 weeks corrected age. At <33 weeks PMA, 96% of GMs were abnormal and 4% normal. At 34 - 37 weeks PMA, 89% of GMs were abnormal and 11% normal. All GMs recorded at term equivalent age were abnormal. At 12 - 14 weeks corrected age, 7% of GMs were abnormal and 93% normal.
Conclusion. GMs were predominantly abnormal prior to term with a significant decrease in abnormality at 12 - 14 weeks corrected age. Lower birthweight and lower PMA were associated with increased odds for abnormal GMs. In a resource-constrained environment, observing GMs at 12 - 14 weeks corrected age (during the fidgety period) is a time- and cost-effective method to determine the risk for adverse neurodevelopment.

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Significant advances in perinatal and neonatal care have improved survival rates for preterm infants. This increase in survival is mirrored by an increase in the risk of motor and cognitive impairment.[1] Early identification and intervention for infants at risk for neurodevelopmental disorders are associated with improved motor developmental outcomes during infancy (0 - ≤3 years), and enhanced cognitive function up to preschool age (3 - ≤5 years).[2] Among the motor impairments reported in preterm infants, cerebral palsy (CP) remains one of the most common,[3] with a higher prevalence of children with CP reported in Africa than the estimated 2 -2.5 cases per 1 000 live births reported in most studies conducted in the USA and Europe.[4,5] Unfortunately, the screening and identification of developmental disabilities in high-risk infants in Africa has been inadequate.[5] Low- and middle-income countries (LMICs) such as South Africa (SA) are unable to provide costly technical evaluation procedures needed to detect brain dysfunction in high-risk infants.[6]

In SA public hospitals, high-risk preterm infants are discharged when they have adequate weight gain and are medically stable, usually at 34 - 36 weeks post menstrual age (PMA) and weighing 1 800 g. These public hospitals have limited available beds and a high patient turnover. Mothers returning with their infants after discharge to impoverished rural areas often have inadequate access to follow-up medical care. As a result, premature infants who are at high risk for neurodevelopmental disorders are often lost to follow-up, medical management and effective interventions. Infants born preterm with undiagnosed CP are therefore at risk for secondary complications such as muscle/tendon contractures, bony torsion, hip displacement and spinal deformities.[7] Therefore, an inexpensive, reliable and non-invasive method for early identification of CP or other neurological disorders is warranted.

Prof. Heinz Prechtl and his co-workers developed such a method in the early 1990s. Prechtl's qualitative assessment of general movements (GMs) is an assessment tool that evaluates the quality of spontaneous movement patterns in infants. The nervous system of the fetus and young infant generates spontaneous movement patterns endogenously, i.e. without being triggered by specific sensory input.[8] From as young as 9 weeks PMA, generalised and very complex movements involving the whole body start to occur. These complex movement patterns are called GMs. They are age-specific, continue after birth and can be observed until 20 weeks post term age, when purposeful antigravity movements start to dominate.[8]

Before term age, GMs are called preterm or fetal movements, from term age until 6 - 9 weeks post term age they are called writhing movements and from 9 weeks until 20 weeks post term they are called fidgety movements.[8] Normal GMs are fluent and elegant and have a complex and variable character.[8] Periventricular brain lesions can lead to a disruption of the corticospinal projections and lead to abnormal GMs, which are movements characterised by a loss of complexity and variability. Abnormal GMs have a monotonous or poor repertoire, or are stiff and cramped, or chaotic.[8] A persistent pattern of cramped synchronised GMs and the absence of fidgety movements are highly predictive for the development of CP.[8] General movement assessments (GMAs) are quick and easy to perform, and are cost-effective compared with other investigations traditionally used, such as magnetic resonance imaging, brain ultrasound and traditional neurological examination.[8] Various systematic reviews have validated the qualitative assessment of GMs as a reliable predictor of CP.[9-11] Their straightforward and easy applicability makes GMAs an ideal tool for assessing the young nervous system, especially in low-resource settings.[6] Studies on GMAs in LMICs are rare,[6] with only one study conducted to date in SA, on GMAs at 12 - 15 weeks post term age.[9]

Although the qualitative assessments of GMs have been widely reported, most studies assessed GMs at 12 - 15 weeks post term age and term age, while only a few studies reported on GM trajectories during preterm age.[12-15] There is therefore a limited understanding of GM trajectories in preterm (32 - 36 weeks PMA), very preterm (28 - 31 weeks PMA) and extremely preterm (<28-week PMA) infants.[15] The high predictive validity of GMs relies on developmental trajectories, since a trajectory of GMAs is more accurate at predicting an infant's neurodevelopmental outcome than single assessments.[8,15] A systematic review found that children born preterm with consistently abnormal GMs up to 8 weeks after term had an intelligence quotient (IQ) of 5 - 13 points lower than that of children whose GMAs normalised after term age.[16] The early neurodevelopment of the preterm infant may be negatively influenced by perinatal factors such as intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia and postnatal corticosteroids.[17,18] Knowledge and understanding of GM trajectories and the effect of adverse perinatal factors is essential to compare and analyse in future studies on the neurodevelopmental outcome of high-risk infants.

The primary aim of the present study was to assess the trajectory of GMs from preterm age until 12 - 14 weeks corrected age in very low-birthweight (VLBW) and extremely low-birthweight (ELBW) infants who were admitted to Tygerberg Children's Hospital (TCH) in Cape Town, SA. The objectives of the study were to describe the association between adverse perinatal factors and GM trajectories.

Methods

Study design and participants

A longitudinal, prospective cohort design with repeated measures was conducted. A successive sampling method was used to recruit preterm infants born before 33 weeks' gestation and weighing <1 500 g, between 1 December 2017 and 1 May 2018, and admitted to the neonatal wards or to the neonatal intensive care unit (NICU) at TCH in Cape Town, SA. The following exclusion criteria applied: infants diagnosed with congenital/chromosomal defects known to affect neurodevelopment (e.g. Down syndrome or Edwards syndrome); infants with birth malformations of the central nervous system (e.g. myelomeningocele); infants diagnosed with congenital disorders (e.g. arthrogryposis multiplex congenital, osteogenesis imperfecta congenital); and infants with microcephaly (≤3rd percentile). The study was approved by the Human Research Ethics Committee of the Faculty of Health Science at Stellenbosch University (ref. no. S17/08/142). Written informed consent was obtained from the parents or legal guardians of the infants enrolled in the study.

Procedure for GMA

Serial GMs were recorded during the following key age periods: 1 - 2 weeks after birth to 33 weeks PMA; 34 - 37 weeks PMA; term equivalent age (TEA) (full term age (39 weeks 0 days - 40 weeks and 6 days PMA) or late term age (41 weeks 0 days - 41 weeks and 6 days PMA)); and 12 - 14 weeks corrected age (fidgety period). Prior to term, GMs were recorded while infants were inpatients at TCH or adjacent hospitals. At TEA, GMs were recorded at surrounding hospitals, or as an outpatient at TCH if the patient has been discharged home. GMs at 12 - 14 weeks corrected age were recorded during the infants' first outpatient follow-up visit at the neonatal high-risk clinic at TCH. Only infants with at least two recorded GMAs were included in the study.

GM assessments were performed using a standardised procedure. A light-sensitive, high-quality camera phone was used directly from above. During all assessments, infants were recorded in supine position and were lightly dressed (thin nappy and vest). Before term, infants were assessed in the crib or incubator, and were videoed for 5 - 10 minutes (depending on how long it took to observe a spontaneous movement sequence). Recordings made during the preterm age were taken during awake and asleep behavioural states of the infant.[8] At TEA and 12 - 14 weeks corrected age, the infants were placed on a unicolour mattress or on the examination bed and videoed for 5 minutes, and recordings were made with the infant in an active alert state, with the absence of crying/fussing.

Assessment and scoring of GMs

GMs were independently scored by at least three qualified assessors with advanced GM certification from the GM trust (http://general-movements-trust.info/5/home). Assessors were blinded to the neonatal history of the infants as well as their previous GMA scores to avoid the assessors being influenced. GMs were assessed using Prechtl's method on the qualitative assessment of GMs.[19] From 1 - 2 weeks after birth (preterm age) until TEA, GMs were scored as follows:

Normal GMs: these movements are characterised by fluency and elegance, involving the whole body. They consist of variable patterns of flexion, extension and rotation of the limbs and rotation of the trunk, and are complex in nature.

Abnormal GMs: these were categorised as:

- poor repertoire: movements that are lacking complexity and speed, amplitude and force, often observed as slower than normal GMs. Movements tend to be repetitive and monotonous.
- cramped-synchronised: these movements are rigid in appearance, involving an almost simultaneous contraction and subsequent relaxation of all limbs and trunk muscles.
- chaotic: movements that are large and abrupt in nature, involving all limbs and lacking fluency and elegance.

At 12 - 14 weeks' corrected age (fidgety period), GMs were scored as follows:

- normal fidgety movements: characterised by small amplitude, moderate speed and variable acceleration of the trunk and limbs in all directions.

- abnormal fidgety movements: these look like normal fidgety movements, but their amplitude, speed and jerkiness are moderately or greatly exaggerated.
- absent fidgety movements: fidgety movements are not observed, but other movements like wiggling-oscillating arm movements, swiping movements of the arms and kicking of the legs can still be observed.

Credibility of analysis

Individual scores were compared within the group. In the case of score discrepancies, Prof. Christa Einspieler, a licensed senior GM Trust tutor, made the final decision.

Perinatal data

Perinatal information from the medical histories and neonatal course of the participating infants was collected. The data included: gestational age; birthweight; gender; ventilation and/or oxygen requirements; the presence of intraventricular haemorrhage or periventricular leukomalacia; necrotising enterocolitis, postnatal infections and HIV exposure.

Statistical analysis

Stata version 14 (StataCorp., USA) and SPSS version 24 (IBM Corp., USA) were used to analyse data. A p-value <0.05 was considered statistically significant. The proportion of infants with normal and abnormal GMs over time was reported at each of the four key time points, along with 95% confidence intervals (CIs). The change from one time point to the next in abnormal GMs was assessed by cross-tabulation of normal and abnormal GMs at adjacent time points, and also from the first time point to the last time point. McNemar's χ^2 test was used to assess statistical significance in the change in proportions between two key time points.

Logistic regression analysis adjusting for within-patient clustering over time was used to estimate the odds ratios and 95% CIs for the effects of time and the various confounding variables for the outcome of abnormal v. normal GMs. The potential confounders included were gestational age, birthweight, gender, type and duration of ventilation, total duration of oxygen via nasal cannula, length of hospitalisation, intraventricular haemorrhage grade III/IV, periventricular leukomalacia grade III/IV, surgical necrotising enterocolitis, postnatal corticosteroids, small for gestational age, any surgical procedure, culture Gram-positive or negative sepsis, meningitis, exposure to HIV and multiple births.

Results

Demographic profile and characteristics of the study population

A total of 119 eligible infants were included in the study. During the course of the study, 12 infants passed away, of whom 9 were male. The majority of included infants were female (53%). The demographic profile and characteristics of the cohort are summarised in Table 1. A total of 300 GMAs were conducted: 110 at <33 weeks PMA, 47 at 34 - 37 weeks PMA, 55 at term age and 88 at 12 - 14 weeks post term age. A flowchart of the study participants and conduction of GMAs is presented in Fig. 1.

Results of GMAs

The GMA score results of the four different key assessment points are illustrated in Table 2. During the first time point (from birth to 33 weeks PMA), 110 infants were assessed, and at the second time point (34 - 37 weeks PMA), 47 infants. At TEA (the third time point) 55 infants were assessed, and during the final time point (12 - 14 weeks corrected age), 88 GMAs were conducted.

Association between perinatal factors and GM outcomes

The association between perinatal risk factors listed in Table 1 and GMs were assessed using a logistic regression model. On univariate analysis, lower birthweight (p=0.043), gestational age at birth (p=0.017), intraventricular haemorrhage grade IV (p<0.001) and time since birth (PMA in weeks) (p<0.001) were associated with increased odds for abnormal GMs. These findings are illustrated in Table 3.

Table 1. Demographic profile and characteristics of the study sample (*N*=119)

Characteristic	*n* (%)*
Male	56 (47)
Female	63 (53)
Gestational age (weeks), mean (SD)	28.6 (1.9)
Birthweight (g), mean (SD)	1 048.2 (206.4)
Length of hospital stay (days), mean (SD)	42.9 (26.8)
Infants who received invasive ventilation	9 (8)
Infants who received non-invasive ventilation	109 (92)
Infants who received oxygen via nasal cannula	91 (76)
IVH grade III	4 (3.4)
IVH grade IV	1 (0.8)
PVL	6 (5)
NEC	16 (13.4)
Antenatal steroids	93 (78.2)
IUGR	23 (19.3)
Anaesthesia	9 (7.6)
Sepsis	37 (31.1)
Meningitis	0 (0)
HIV exposure	27 (22.7)
Twin births	20 (16.8)

SD = standard deviation; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; NEC = necrotising enterocolitis; IUGR = intrauterine growth restriction.
*Unless otherwise indicated.

Table 2. General movement assessment (GMA) results at key time points

Key time point	GMA	*n* (%)
Birth to 34 weeks PMA	Normal	4 (3.6)
	Poor repertoire	105 (95.5)
	Cramped-synchronised	1 (0.9)
	Total abnormal	106 (96.4)
34 weeks PMA	Normal	5 (10.6)
	Poor repertoire	40 (85.1)
	Cramped-synchronised	2 (4.3)
	Total abnormal	42 (89.4)
Term age	Normal	0 (0)
	Poor repertoire	54 (98.2)
	Cramped-synchronised	1 (1.8)
	Total abnormal	55 (100)
12 - 14 weeks corrected age	Normal fidgety	82 (93.2)
	Absent fidgety	6 (6.8)
	Total abnormal	6 (6.8)

PMA = post menstrual age.

Lower birthweight, gestational age at birth, intraventricular haemorrhage grade IV, and time since birth (PMA in weeks) were included in a multivariable analysis. Since birthweight and gestational age were highly correlated and thus collinear, gestational age was dropped from the final model.

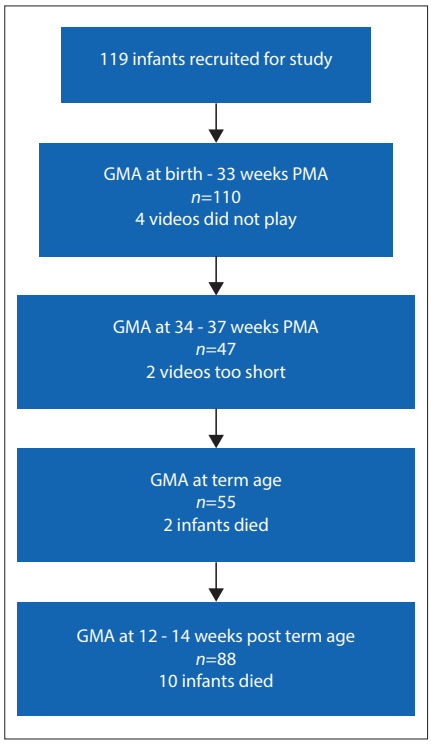

Fig. 1. Flowchart of general movement assessments (GMAs) from birth to 12 - 14 weeks post term age. (PMA = post menstrual age.)

Birthweight (p=0.046) and time (PMA in weeks) (p<0.001) were the only variables that remained significantly associated with abnormal GMs after adjustment for confounding variables listed in Table 1.

Discussion

The quality of spontaneous movement patterns observed in infants reflects the integrity of the young nervous system and serves as a predictor for later neurological outcomes.[8] Although the assessment of GMs has been utilised for over 25 years, to date, only six studies globally have reported on preterm and post-term GMA trajectories at the following key time points: preterm, term age (37 - 42 weeks PMA) and 12 - 15 weeks post term age.[20-25] The present study is the first such study conducted in Africa to describe the quality of GM trajectories in infants born before 33 weeks' gestational age till 12 - 14 weeks corrected age in VLBW and ELBW infants. The findings of the current study demonstrate that the majority of infants displayed abnormal GMs during preterm assessments. These results are consistent with the findings from previous studies that reported on at least two GMAs prior to term age in VLBW and ELBW infants.[12-15]

In the present study, no infants displayed normal GMs at term age. This increased proportion of abnormal GMs from preterm to term age differs from what was found in previous studies that reported on GMs from preterm to term age.[12,15,24,26] A possible explanation may be that, in the current study, the birthweight of 85% of the infants assessed at term age was <1 200 g. Furthermore, 73% of infants had a gestational age of <29 weeks. Both a lower birthweight and gestational age have been significantly associated with abnormal GMs at term age.[27] Another reason for not observing any normal GMs at term age is the difficulty with follow-up of infants who were discharged (see limitations). Most infants with recorded GMs at term were still admitted at term age. This likely reflects the extent of neonatal problems encountered by term-age infants who were still hospitalised. They would therefore be a high-risk cohort for neurodevelopmental disorders or other health-related disorders.

Our finding that none of the infants in the current study displayed abnormal fidgety movements at 12 - 14 weeks corrected age is similar to findings by other researchers.[28-30] Abnormal fidgety movements are extremely rare and of low predictive value.[19,31] In the current study, 7% of infants had absent fidgety movements at 12 - 14 weeks corrected age, which is lower than the 9% reported in a previous study conducted at TCH on 115 VLBW preterm infants.[7] Other studies that included both high- and low-risk infants reported higher percentages of infants with absent fidgety movements.[28-30,32,33]

The significant decrease in the proportion of infants who displayed abnormal GMs from the first GMA (n=73) to the final GMA (n=5) is consistent with previous published findings.[22,24,26] GMs assessed during the fidgety period have a higher yield and are more feasible in a resource-constrained setting.

Influence of perinatal variables on GMs

Multivariable analysis of the association between certain perinatal risk factors and GM trajectories identified that an increase in birthweight and time (indicated as PMA in weeks) was inversely associated with an abnormal GM trajectory. This differs from what was reported in other studies.[15,26] Olsen *et al.*[15] reported infection as an independent variable associated with an increased risk for abnormal GMs. Zahed-Cheick *et al.*[26] found in a group of extremely preterm infants that gestational age at birth, nosocomial infections, chronic lung disease and patent ductus arteriosus were associated with abnormal preterm GMs. However, at 12 - 14 weeks corrected age, only gestational age at birth was correlated with absent fidgety movements, while no correlation with birthweight was found.[26]

Table 3. Univariate analysis of perinatal risk factors for abnormal general movements

Risk factor	Odds ratio (95% CI)	z-score	p-value
Time	0.098 (0.04 - 0.25)	−4.78	0.000
Birthweight	0.99 (0.998 - 0.999)	−2.03	0.043
Gender	1.27 (0.91 - 1.78)	1.39	0.164
HIV exposure	1.48 (0.95 - 2.31)	1.72	0.086
GA at birth	0.91 (0.85 - 0.98)	−2.39	0.017
Length of hospital stay	1.01 (0.99 - 1.01)	1.61	0.108
Non-invasive ventilation	1.32 (0.87 - 2.01)	1.32	0.187
Invasive ventilation	0.68 (0.35 - 1.36)	−1.08	0.281
Nasal oxygenation	1.01 (0.99 - 1.02)	1.19	0.236
IVH gr III	1.02 (0.70 - 1.47)	0.09	0.930
IVH gr IV	0.43 (0.37 - 0.51)	−9.54	0.000
PVL	1.09 (0.48 - 2.50)	0.21	0.834
NEC	1.35 (0.86 - 2.12)	1.31	0.189
IUGR	1.18 (0.79 - 1.76)	0.81	0.421
Antenatal steroids	1.13 (0.77 - 1.65)	0.60	0.546
Anaesthesia	1.42 (0.86 - 2.35)	1.35	0.176
Sepsis	1.09 (0.78 - 1.53)	0.52	0.600
Twin births	1.39 (0.92 - 2.09)	0.59	0.111

CI = confidence interval; GA = gestational age; IVH: intraventricular haemorrhage; PVL = periventricular leukomalacia; NEC = necrotising enterocolitis; IUGR = intrauterine growth restriction.

The results of the current study are consistent with the findings of a recent study[27] that reported a lower birthweight to be associated with abnormal GMs at term age and 12 - 14 weeks corrected age. To the best of our knowledge, our study is the largest to date to report on GM trajectories measured at four key time points. This might explain why the study is the first to report on time (PMA in weeks) as a significant variable associated with GM outcome. De Vries *et al.*[13] recorded serial GMs during the first 10 days of life in very preterm and extremely preterm infants. They found that abnormal GMs were significantly related to preterm age. The younger the infants (PMA), the more often they presented with abnormal GMs. They concluded that an improvement in GM trajectories during the first week occurred in infants who had a higher birthweight and gestational age.

The present study is unique as 23% (n=27) of the cohort were HIV-exposed but uninfected. On univariable analysis, HIV exposure during pregnancy was not significantly associated with an abnormal GM trajectory. The quality of GM trajectories and neurological outcome in HIV-exposed but uninfected as well as exposed and infected children is a largely under-researched field. Only one previous study has reported on GMs in a HIV-exposed cohort.[34] The authors found that comorbid HIV and maternal opiate exposure were associated with an abnormal GM trajectory from term age till 5 months post term age, and that infants with HIV infection did not differ from HIV-exposed but uninfected infants with respect to their GM quality. A large prospective study found that maternal opioid use is associated with inadequate antenatal care and a higher likelihood of poor nutrition and polysubstance use, including alcohol, cigarettes, marijuana and stimulants. Consequently, prenatal opioid exposure was associated with poor birth outcomes and adverse childhood physical health and neurodevelopmental outcomes.[35] A systematic review found that once confounders such as maternal substance misuse were accounted for, studies did not demonstrate developmental delays in HIV-exposed, uninfected infants up to the age of 2 years.[36] Since most of the evidence came from high-income countries, the researchers suggested that other factors such as poverty and early infant malnutrition and growth in low-resource settings may affect neurodevelopment of HIV-exposed, uninfected infants.[36]

Previous studies have reported intraventricular haemorrhage (IVH) grade III and IV to be associated with abnormal GM trajectories in preterm infants.[15,33] The small sample size of infants in the present study diagnosed with IVH grade III and IV may explain why IVH was not significantly associated with abnormal trajectories. Although sepsis was not significantly associated with abnormal GMs, previous studies[15,26] have reported an association between post-natal infections and abnormal GMs. Evidence on the significance of infection on GM outcome remains conflicting.

Study limitations

The main limitation of the study was the significant decrease in the number of GMAs done from the first assessment (birth to 33 weeks PMA) (n=110) to the second assessment (34 - 37 weeks PMA) (n=47) and term age assessments (n=55). At TCH, once medically stable, infants are transferred to district hospitals and other lower care facilities, or discharged home. Owing to the fact that most infants were discharged from hospital before the second assessment, follow-up appointments had to be arranged. During the course of the study, the City of Cape Town was plagued by major bus and taxi strikes as well as protest actions. Since most of the parents/guardians made use of public transport and their safety could not be guaranteed, a large proportion of infants was unable to attend their preterm and term age follow-up assessments. Public transport is also costly, and given that most of the population comes from a lower socioeconomic background, many parents were unable to bring their infants in for a term age GMA. Parents of discharged infants who were not able to attend follow-up appointments were asked to send a video recording of their infant via WhatsApp, and were compensated for their data usage. However, not all parents had access to smartphones and WhatsApp, or the cellphone recordings were of such low quality that it was not possible to assess the video recording of GMs. A large number of infants with 34 - 37 weeks PMA and term GMAs were still hospitalised. Since these infants had a more complicated medical history, this might explain the reduced number of normal GMs observed at 34 - 37 weeks PMA, as well as the absence of normal GMs at term age.

Notwithstanding the setback of follow-up at preterm and term age, 88 infants were assessed at 12 - 14 weeks corrected age, and a total of 300 assessments were conducted over the four key time periods.

In the present study, individual infant trajectories were not described. Individual trajectories, especially for infants displaying temporary normal or cramped-synchronised GMs prior to term or at term age, may provide a better understanding of the relationship between perinatal risk factors and GM quality. Furthermore, infants were only assessed until 12 - 14 weeks corrected age. Although it was not part of the scope of the current study, neurological assessments conducted at 12 and 24 months corrected age may be of value to describe the effect of GM trajectories and perinatal risk factors on long-term neurodevelopmental outcomes.

Clinical and research implications

Heinz Prechtl and his colleagues encouraged the use of serial assessments to provide a comprehensive portrayal of the infants' neurodevelopmental trajectory.[19] However, the results of the present study indicate that assessment of preterm and term GM trajectories does not necessarily enable earlier identification of infants at risk for neurodevelopmental difficulties in our study population. In a low-resource setting, it is therefore not clinically useful to allocate time and resources to conduct preterm and term age GMs, as they are likely to be abnormal and transition to normal over time. High-risk preterm infants in low- and medium-resource settings should rather be assessed at 12 - 14 weeks corrected age, as has previously proven to be of high predictive value at TCH.[7] Furthermore, infants with a lower birthweight should be targeted for more frequent follow-up, as they remain the highest risk group for neurological deficits.

The study cohort will be followed up to determine the relationship between GM trajectories and long-term neurodevelopment. Future research should describe individual infant trajectories together with long-term neurological follow-up in order to establish the influence of perinatal factors on long-term outcome.

Conclusion

Using trajectories of GMs is a novel way of tracking the integrity of the developing neurological system. In resource- and time-constrained settings such as SA, it is important to evaluate the feasibility of such an approach. Our study demonstrates that most GMs have normalised by the fidgety movement period, and it is therefore more feasible for the group (but not the individual infant) to do GMAs at 12 - 15 weeks post term. Lower birthweight and lower PMA (time) were associated with increased odds for abnormal GMs. Infants with a lower birthweight should be targeted for early (at 12 - 14 weeks corrected age) and frequent follow-up as they remain the most at-risk group for neurological deficits.

Declaration. This research was submitted in partial fulfilment of the requirements or the degree of Masters of Physiotherapy in the Faculty of Medicine and Health Sciences at Stellenbosch University(Paed).

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Author contributions. RK was the main author and was responsible for data collection. RK, MB, JCFdP and JIvZ were responsible for the conceptualisation of the study design. MB, JCFdP and JIvZ were responsible for the GMAs. RK, MB, JCFdP and JIvZ were responsible for data analysis and interpretation. RK was responsible for writing and MB, JCFdP and JIvZ for editing of the manuscript.

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Anaemia, iron and vitamin A status among South African school-aged children living with and without HIV

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Background. Data on iron and vitamin A deficiency are scarce in school-aged children living with HIV (HIV+) compared with children without HIV (HIV−). Both deficiencies can contribute to anaemia.
Objective. To assess anaemia, iron and vitamin A status in a sample of HIV+ and HIV− school-aged children in South Africa.
Methods. In this comparative cross-sectional study, biomarkers for anaemia (haemoglobin), iron (plasma ferritin (PF), soluble transferrin receptor), vitamin A (retinol-binding protein (RBP)) and inflammatory status (C-reactive protein, α-1-acid glycoprotein) were measured in 8 - 13-year-old children from Cape Town living with (*n*=143) and without HIV (*n*=148). Measurements of PF and RBP were adjusted for inflammation using a regression-correction approach.
Results. HIV+ children had higher prevalences of anaemia (29% v. 14%; odds ratio (OR) = 2.6; 95% confidence interval (CI) 1.4 - 4.9; *p*=0.002), iron-deficient erythropoiesis (20% v. 9%; OR=2.5; 95% CI 1.2 - 5.0; *p*=0.013) and iron deficiency anaemia (11% v. 4%; OR=2.9; 95% CI 1.1 - 7.7; *p*=0.035) than HIV− children. Marginal vitamin A deficiency was noted in 52% of HIV+ and 57% of HIV− children (*p*=0.711). Subclinical inflammation was more prevalent in HIV+ than HIV− children (*p*=0.012).
Conclusion. Anaemia, iron-deficient erythropoiesis and iron deficiency anaemia were more prevalent in HIV+ than HIV− children. Prevalence of marginal vitamin A deficiency was high in both groups. Efforts to improve micronutrient status and mitigate nutritional determinants of anaemia in HIV+ children from resource-limited settings should be prioritised.

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Sub-Saharan Africa has the largest HIV burden globally.[1] In South Africa (SA), an estimated 260 000 children <15 years of age are living with HIV (HIV+), with 14 000 new infections recorded in this age group in 2018,[1] despite vertical HIV transmission prevention programmes.[2] Anaemia is a frequent haematological comorbidity of HIV infection, with a complex and multifactorial aetiology.[3] Although chronic inflammation and antiretrovirals such as zidovudine may cause anaemia in HIV+ individuals, nutritional determinants such as iron and vitamin A deficiencies are likely in resource-limited settings where inadequate dietary intake may be common.[4,5]

Anaemia is characterised by a lower-than-normal haemoglobin (Hb) concentration.[6] Iron deficiency and anaemia can prevent children from reaching their developmental and scholastic potential, thereby limiting long-term work opportunities and quality of life.[7,8] As anaemia is a risk factor of all-cause mortality in HIV+ individuals despite their receiving antiretroviral therapy (ART), knowledge on best strategies to abate this comorbidity is much needed.[9]

Iron and vitamin A deficiencies in SA school-aged children are estimated at 13.7% and 12.2%, respectively.[10] National prevalence rates are not stratified by HIV status and estimates of these nutritional deficiencies among HIV+ school-aged children derive from only a few small, independent studies.[11,12]

Assessing iron and vitamin A status in HIV+ individuals is challenged by the effects of inflammation on conventional biomarkers. Plasma ferritin (PF), a positive acute-phase reactant, is elevated during inflammation and so could potentially mask depleted iron stores. Retinol-binding protein (RBP), a negative acute-phase reactant, is lowered in the presence of inflammation and so could potentially lead to vitamin A deficiency being overreported.[13]

Different approaches are available for using inflammation-sensitive biomarkers to assess micronutrient status. These include raising or lowering the cut-off values that define deficiency, excluding individuals with elevated inflammatory markers such as C-reactive protein (CRP) or α-1-acid glycoprotein (AGP), arithmetic approaches with fixed categorical correction factors and, more recently, a regression correction approach.[14] The advantage of using a regression correction approach as suggested by the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) group is that adjustments correspond to the magnitude of inflammation (measured by CRP or AGP) and reflect acute-phase reactant estimates better than other methods.[13]

To our knowledge, iron and vitamin A status among school-aged HIV+ children have not been assessed using inflammation-adjusted biomarkers and compared with that of children without HIV (HIV−). The prevalence of iron and vitamin A deficiencies and their contribution to anaemia in HIV+ individuals therefore remain unclear. In this study, we assessed anaemia, iron and vitamin A status among a sample of HIV+ and HIV− school-aged children in SA.

Methods

Study design and participants

For this comparative cross-sectional study, we used data collected at the initial screening visits that formed part of a series of iron studies at the Family Centre for Research with Ubuntu (FAMCRU) in Cape Town, SA. Both HIV+ and HIV− children were recruited from the FAMCRU patient database, Tygerberg Hospital's Infectious Diseases Outpatient Unit, and through word of mouth from similar communities across Cape Town. Children had to be between 8 and 13 years old, without acute illness at the time, and should not have used iron-containing supplementation in the three months prior to the study. Routine blood work records for HIV+ children were accessed on the National Health Laboratory Service's electronic portal to confirm that they were in HIV care. The absence of HIV infection was confirmed with a rapid HIV assay (First Response HIV Card 1–2.0, Premier Medical Corporation, India) in the HIV− group. Between September 2018 and August 2019, children were screened for the series of iron studies until four equal groups of 45 children per group were enrolled by HIV and iron status (N=180).[15] This sample was attained after 293 screenings. Anthropometric and biochemical indices of anaemia, iron status, vitamin A status and inflammation were measured in all 293 children and were used for this comparative cross-sectional study. Owing to insufficient blood volume in two children, 291 children's samples were included in the analyses. With an 80% power and a type I error rate of 5% assumed, the final sample size allowed for detecting a medium effect size of 0.24 between groups. Sociodemographic and selected HIV care information were collected only for the abovementioned subgroup (n=180).

Participant and sociodemographic information

Height and weight were measured using a Micro 1023 electronic platform scale and stadiometer (Scalerite, SA) and standardised techniques.[16] In the HIV+ group, the most recent HIV viral load result was obtained from the National Health Laboratory Service's electronic portal. Sociodemographic and HIV care information were obtained using a structured questionnaire.

Laboratory analyses

Hb concentrations were measured in whole blood on the day the blood sample was drawn using a Siemens Advia 2120i Haematology System (Siemens, Germany). Plasma was separated out, aliquoted to allow for measuring iron, vitamin A and inflammation markers, and then frozen at −70°C. Iron, vitamin A and inflammation status were measured using a multiplex immunoassay previously described (biomarkers included: PF and soluble transferrin receptor (sTfR) for iron status; RBP for vitamin A status; and CRP and AGP for inflammation).[17]

Data management and definitions

Data were collected and managed using the Research Electronic Data Capture (REDCap) tools hosted at the ETH Zurich. Height-for-age z-scores (HAZ) and body mass index-for-age z-scores (BAZ) were calculated using AnthroPlus Software Version 1.0.4 (World Health Organization, Switzerland).

Anthropometric definitions were as follows:[18] atunting: HAZ<−2; healthy weight: −2≤BAZ≤1; underweight: −3<BAZ≤−2; severe underweight: BAZ<−3; overweight: 1<BAZ≤2; obesity: BAZ>2.

Anaemia was defined as Hb<11.5 g/dL for children 8 - 11 years old and Hb<12 g/dL for children 12 - 13 years old (mild anaemia: 11≤Hb≤11.4 g/dL for children 8 - 11 years old and 11≤Hb≤11.9 g/dL for children 12 - 13 years old; moderate anaemia: 8≤Hb≤10.9 g/dL; severe anaemia: Hb<8 g/dL).[6]

We adjusted PF and RBP values for inflammation based on CRP and AGP concentrations (along a continuous scale) using the BRINDA regression correction approach. Lower reference values for CRP and AGP were −2.26 ln (mg/L) and −0.52 ln (g/L), equating to 0.1 mg/L and 0.59 g/L, respectively.[13] The correction was therefore applied only to children with CRP and AGP concentrations above the reference values.

Iron deficiency (ID) was defined as inflammation-adjusted PF<15 µg/L.[14] Iron-deficient erythropoiesis was defined as sTfR>8.3 mg/L.[17] Iron deficiency anaemia (IDA) was defined as concomitant anaemia and ID or iron-deficient erythropoiesis.

Marginal vitamin A deficiency was defined as inflammation-adjusted RBP concentrations of 0.7 - 1.05 µmol/L and established vitamin A deficiency as inflammation-adjusted RBP<0.7 µmol/L.[19]

The presence of inflammation was classified as CRP≥5 mg/L or AGP>1 g/L. Subclinical inflammation was classified a priori as CRP concentrations of 0.05 - 4.99 mg/L, reflecting detectable CRP concentrations but below the clinically used threshold for acute infection.

Statistical analyses

Statistical analyses were performed using SPSS version 27 (IBM Corp., USA). Participant characteristics were summarised using descriptive statistics. Categorical variables are reported as frequencies and percentages. The prevalence of unknown parameters are reported as estimates within 95% confidence intervals (CIs).

The distribution of continuous variables was investigated using the Shapiro-Wilk test. Homogeneity of variance was tested with Levene's test. Normally distributed continuous variables are reported as means and standard deviations (SDs), and non-normally distributed continuous variables are reported as medians and interquartile ranges (IQRs).

For participant and sociodemographic information, between-group differences were assessed using the independent samples t-test or Mann-Whitney U-test for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables.

For anaemia, iron, vitamin A and inflammatory status, between-group differences were assessed using analysis of covariance (ANCOVA) for log-transformed continuous outcome variables, and binary logistic regression for categorical outcome variables, adjusting for age and sex. We report adjusted odds ratios (ORs) and 95% CIs for the logistic regression parameters. Statistical significance was set at p<0.05.

Ethical considerations

The study protocol was approved by the health research ethics committees of Stellenbosch University (ref. no. S18/06/136 and M18/05/017) and the ETH Zurich (ref. no. EK 2018-N-40). Assent was obtained from all children, and consent from their caregivers (parent or legal guardian).

Results

Participant characteristics and sociodemographic indicators

In total, 293 children were screened for participating in the series of iron studies (HIV+, n=144; HIV−, n=149) and being included in this comparative cross-sectional analysis. As one child from each group was excluded for insufficient blood volume, analyses were performed on 291 records.

Table 1 presents participant characteristics (N=291) and selected indicators collected from the subgroup of 180 children described above. The group of HIV+ children was older (p=0.004) and more

Table 1. Sociodemographic characteristics of participants (*N*=291)

Variables	HIV+ (*n*=143)	HIV– (*n*=148)	*p*-value
Sex, *n* (%)			
Male	75 (52)	71 (48)	
Female	68 (48)	77 (52)	0.45
Age (years), median (IQR)	11.5 (9.9 - 12.3)	10.8 (9.5 - 12.0)	0.004
Age (years), *n* (%)			
8	20 (14)	29 (20)	
9	16 (11)	23 (15)	
10	19 (13)	32 (22)	
11	42 (30)	28 (19)	
12	26 (18)	30 (20)	
13	20 (14)	6 (4)	0.005
Height-for-age *Z*-score, mean (SD)	–1.33 (1.01)	–0.56 (1.04)	<0.001
Stunted, *n* (%)	37 (26)	16 (11)	0.001
Body-mass-index-for-age *Z*-score, mean (SD)	–0.41 (1.10)	–0.14 (1.32)	0.07
Healthy weight, *n* (%)	124 (87)	117 (79)	0.08
Underweight, *n* (%)	5 (4)	5 (3)	1.00
Severe underweight, *n* (%)	1 (1)	3 (2)	0.62
Overweight, *n* (%)	9 (6)	16 (11)	0.17
Obesity, *n* (%)	4 (3)	7 (5)	0.39
HIV viral load, *n* (%)			
<50 copies/mL	122 (85)	-	-
≥50 copies/mL	21 (15)	-	-
Subgroup	*n*=90	*n*=90	
Age at start of antiretroviral therapy (years),* median (IQR)	1 (0 - 2)	-	-
Current antiretroviral regimen			
ABC-3TC-LPV/r	45 (50)	-	-
ABC-3TC-EFV	20 (22)	-	-
AZT-3TC-LPV/r	17 (19)	-	-
AZT-3TC-NVP	3 (3)	-	-
Other	5 (6)	-	-
Relationship status of primary caregiver, *n* (%)			
Single	48 (53)	58 (64)	
In partnership	42 (47)	32 (36)	0.13
Type of housing, *n* (%)			
Formal	53 (59)	62 (69)	
Informal	37 (41)	28 (31)	0.16
Individuals in household, *n* (%)			
2 - 4	37 (41)	23 (26)	
5 - 8	46 (51)	59 (66)	
9 - 15	7 (8)	8 (9)	0.08
Employment status of household breadwinner, *n* (%)			
Permanent	25 (28)	36 (40)	
Temporary	25 (28)	18 (20)	
Unemployed	40 (44)	36 (40)	0.27
Monthly household income, *n* (%)			
<ZAR2 000	47 (52)	46 (51)	
ZAR2 000 - ZAR5 000	14 (16)	16 (18)	
>ZAR5 000	2 (2)	9 (10)	
Did not disclose	27 (30)	19 (21)	0.23
Household receives government grant, *n* (%)	83 (92)	79 (88)	0.32
Child accesses school nutrition programme, *n* (%)	79 (88)	64 (71)	0.006

IQR = interquartile range; SD = standard deviation; ABC = abacavir; 3TC = lamivudine; LPV/r = lopinavir boosted with ritonavir; EFV = efavirenz; AZT = zidovudine; NVP = nevirapine.
*Data available for *n*=85 as start date unknown for five children.

stunted (p=0.001) than the HIV− children. Routine blood work records showed that 85% of HIV+ children had achieved viral suppression. Significantly more HIV+ than HIV− children accessed the National School Nutrition Programme (p=0.006). Other sociodemographic characteristics were similar between the two groups.

Anaemia, iron, vitamin A and inflammatory status

Table 2 compares the anaemia, iron, vitamin A and inflammatory status of HIV+ and HIV− children. Hb concentrations were significantly lower in HIV+ children, with anaemia presenting in 29% (95% CI 21 - 37) of this group compared with 14% (95% CI 9 - 20) of HIV− children (OR=2.6; 95% CI 1.4 - 4.9; p=0.002). The prevalence of ID (adjusted PF<15 µg/L) was 15% (95% CI 9 - 22) in the HIV+ group and 11% (95% CI 6 - 17) in the HIV− group (p=0.515). sTfR concentrations were significantly higher in the HIV+ children, with the prevalence of iron-deficient erythropoiesis at 20% (95% CI 13 - 27) in this group, compared with 9% (95% CI 5 - 15) in the HIV− group (OR=2.5; 95% CI 1.2 - 5.0; p=0.013). Of the HIV+ participants, 11% (95% CI 7 - 18) had IDA, compared with 4% (95% CI 2 - 9) of the HIV− children (OR=2.9; 95% CI 1.1 - 7.7; p=0.035). This accounted for 39% of all anaemia in the HIV+ group and 30% in the HIV− group.

Vitamin A status was similar between the HIV+ and HIV− children. Although established vitamin A deficiency was noted in 9% of both the HIV+ and HIV− children, marginal vitamin A deficiency was seen in 52% (95% CI 43 - 60) and 57% (95% CI 48 - 65) of the HIV+ and HIV− children, respectively (p=0.711). Co-existing vitamin A deficiency (marginal or established) was noted in 50 of the 61 anaemic children (82%), but there was no significant difference according to HIV status (p=0.071) (data not shown). The prevalence of co-existing ID or iron-deficient erythropoiesis and vitamin A deficiency (marginal or established) was higher in the HIV+ than the HIV− group (18% v. 9%; OR=2.2; 95% CI 1.07 - 4.6; p=0.032) (data not shown).

CRP concentrations were significantly higher in the HIV+ group and subclinical inflammation (CRP between 0.05 and 4.99 mg/L) was also more prevalent among these children (p=0.012).

Discussion

This comparative cross-sectional study showed a significantly higher prevalence of anaemia, iron-deficient erythropoiesis and IDA in HIV+ than in HIV− school-aged children in our sample. Marginal vitamin A deficiency was common and similar in the two groups.

The prevalence of anaemia (29% in HIV+ children; 14% in HIV− children) represents a public health problem of moderate (20 - 39.9%) and mild (5 - 19.9%) concern.[6] Anaemia is a common comorbidity of HIV infection and is generally more prevalent in HIV+ than HIV− individuals,[3] as also seen in our study. Promisingly, a recent systematic review and meta-analysis among HIV+ children from Ethiopia reported significantly lower HIV–anaemia comorbidity in ART-treated children compared with ART-naive children.[20]

Alongside the ART programme roll-out and expansion in SA, iron status among SA school-aged HIV+ children appears to be improving. In 2009, Steenkamp *et al.*[11] reported high prevalences of anaemia (60%), ID (30%) and established vitamin A deficiency (63%) in ART-naive children between 1 and 10 years of age. By 2013, Kruger *et al.*[12] reported lower prevalences of anaemia (32%) and iron-deficient erythropoiesis (15%) in children between

Table 2. Status of anaemia, iron deficiency, vitamin A deficiency and inflammation among participants, according to relevant haematological markers (N=291)

Haematological markers for physiological status	HIV+ (n=143)	HIV− (n=148)	p-value
Anaemia			
Haemoglobin (g/dL), median (IQR)	12.1 (11.6 - 12.9)	12.5 (12.0 - 13.2)	0.002
All anaemia, *n* (%)	41 (29)	20 (14)	0.002
Mild	25 (18)	14 (10)	0.046
Moderate	16 (11)	5 (3)	0.012
Severe	0	1 (1)	-
Iron status			
PF (unadjusted) (µg/L), median (IQR)	35.6 (21.6 - 53.7)	34.6 (23.3 - 55.8)	0.76
PF (adjusted) (µg/L), median (IQR)	33.0 (19.6 - 48.9)	32.5 (22.1 - 49.7)	0.63
Iron deficiency, *n* (%)	21 (15)	16 (11)	0.52
Plasma sTfR (mg/L), median (IQR)	6.6 (5.6 - 8.0)	6.1 (5.1 - 7.1)	<0.001
Iron-deficient erythropoiesis, *n* (%)	28 (20)	13 (9)	0.013
Iron deficiency anaemia, *n* (%)	16 (11)	6 (4)	0.035
Vitamin A status			
Plasma RBP (unadjusted) (µmol/L), median (IQR)	0.95 (0.79 - 1.11)	0.94 (0.79 - 1.10)	0.70
Plasma RBP (adjusted) (µmol/L), median (IQR)	0.97 (0.81 - 1.12)	0.96 (0.80 - 1.12)	0.91
Marginal vitamin A deficiency, *n* (%)	74 (52)	84 (57)	0.71
Established vitamin A deficiency, *n* (%)	13 (9)	13 (9)	0.91
Inflammatory status			
Plasma CRP (mg/L), median (IQR)	0.13 (0.02 - 1.16)	0.04 (0.02 - 0.40)	0.024
0.05 <CRP≤4.99 mg/L, *n* (%)	66 (46)	49 (33)	0.012
CRP ≥5 mg/L, *n* (%)	16 (11)	8 (5)	0.11
Plasma AGP (g/L), median (IQR)	0.58 (0.46 - 0.77)	0.51 (0.42 - 0.78)	0.54
AGP >1 g/L, *n* (%)	19 (13)	21 (14)	0.92

IQR = interquartile range; sTfR = soluble transferrin receptor; PF = plasma ferritin; RBP =retinol-binding protein; CRP = C-reactive protein; AGP = α-1-acid glycoprotein.

3 and 14 years old receiving ART. The prevalences of anaemia and iron-deficient erythropoiesis in HIV+ children in our study correspond to those of the latter study. However, the earlier studies referred to here did not compare their findings to HIV− children and our study has subsequently revealed that HIV+ children have significantly higher odds of presenting with iron-deficient erythropoiesis (OR=2.5; p=0.013) and IDA (OR=2.9; p=0.035). The prevalence of IDA was higher than national estimates (2%) for children between 7 and 9 years old in both groups.[10] This may be explained, at least in part, by the use of different definitions, as the mentioned national survey used serum ferritin as the only iron marker and values were not adjusted for inflammation, as we have done.

The prevalence of vitamin A deficiency (whether marginal or established) did not appear to be affected by HIV status and corresponds with national estimates for children between 7 and 9 years old (marginal: 49.9%; established: 12.2%).[10] National vitamin A supplementation programmes target younger children and the vitamin A status of school-aged children largely depends on sufficient dietary intake. In our study, the majority of anaemic children had established or marginal vitamin A deficiency, whereas significantly more HIV+ than HIV− children were affected by co-existing ID or iron-deficient erythropoiesis and vitamin A deficiency. Multiple deficiencies tend to cluster in individuals with micronutrient-poor diets and the synergistic effect of these deficiencies is important in the development of anaemia.[7]

Iron-deficient erythropoiesis and IDA can result from inadequate nutrient intake and absorption-inhibiting factors in the meal matrix, as well as from inflammation-induced hepcidin upregulation, which compromises not only iron mobilisation from macrophages and hepatic iron stores but also dietary iron absorption.[8] Vitamin A deficiency can result from inadequate dietary intake and may also modulate iron metabolism and dysregulate erythropoiesis.[5] Many SA children consume a plant-based staple diet.[21] The bioavailability of non-haem iron and provitamin A (beta-carotene) in plant sources is poor, and absorption-inhibiting components such as phytic acid and polyphenols are high.[22] Although ART reduces comorbidity risk, and treatment regimens continue to improve in order to minimise side-effects, ART alone cannot ameliorate all health risks associated with HIV and persistent subclinical inflammation remain,[3] as also demonstrated by our study. Dietary intake is a modifiable factor, and it remains important to prioritise dietary interventions alongside ART to mitigate nutritional determinants of anaemia in HIV+ children.

Anthropometric assessments highlighted that stunting occurred among significantly more HIV+ than HIV− children. Irreversible height deficits often reflect chronic undernutrition during early life.[23] In cohort studies where early growth deficits affected more HIV+ than HIV− infants,[24,25] the greatest risk factors among HIV+ children were advanced maternal HIV disease, formula feeding and gastrointestinal comorbidities,[24] which conform to the basic causes of stunting, namely poor maternal health and nutrition during pregnancy and inadequate nutrition or recurring infections during early childhood.[23] The children in our study (8 - 13 years old) were born before the rapid scale-up of vertical HIV transmission prevention programmes, HIV testing at birth, rapid initiation of ART and consolidated breastfeeding recommendations in SA.[2] These policy changes may improve early growth outcomes by supporting maternal health, safeguarding breastfeeding practices and enabling early disease control among HIV+ children.

Study strengths limitations

Our findings should be interpreted in context of the study's strengths and limitations. The use of PF and sTfR to assess iron status improves the sensitivity and specificity of iron status estimates. The BRINDA regression correction approach incorporates the magnitude of inflammation measured by CRP and AGP, allowing for more precise adjustments to better reflect acute-phase protein estimates (PF and RBP).[13]

A limitation of the cross-sectional design is that observed associations cannot conclusively be used to comment on causality. Dietary intake was not included during the assessment, which could have assisted in explaining between-group differences in iron status. However, in the subsample enrolled according to HIV and iron status, where dietary intake was explored[15] and compared with HIV− peers, HIV+ children had significantly lower daily intake of highly bioavailable haem iron. Dietary vulnerability to poor iron status in the sample of children in our study therefore appears likely.

Finally, this sample represented children from an urban SA setting and findings may differ in rural and other settings, where habitual dietary intake differs.

Conclusion

Anaemia, iron-deficient erythropoiesis and IDA were more prevalent in HIV+ than HIV− children. The prevalence of marginal vitamin A deficiency was high in both groups. Efforts to improve micronutrient status and mitigate nutritional determinants of anaemia in HIV+ children from resource-limited settings should be prioritised. Studies in rural settings and other provinces are recommended to improve understanding of anaemia and micronutrient deficiencies among school-aged HIV+ children at country level.

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Author contributions. CG is the first author of the paper and was involved in all aspects of the study, from conceptualisation, acquiring funding (with input from MBZ) and developing the methodology to data acquisition, curation, analysis and interpretation. RB and JB assisted with conceptualisation and methodology development, together with input from SLB, MFC and MBZ. NM assisted with data curation and analysis, supported by JB. All authors contributed to reviewing and refining the manuscript for publication.

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Conflicts of interest. None.

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Child development at age 5 years: The effects of maternal education, socioeconomic status and early-life growth examined prospectively in a low-resource setting

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Background. Deeper insight into relationships between social factors and early childhood growth and development is required, particularly in low-resource settings.
Objectives. To determine (*i*) associations between early linear growth and child development at 5 years; and (*ii*) whether early childhood growth mediates relationships between maternal education, household socioeconomic status (SES) and subsequent child development.
Methods. This study used data from the Birth to Twenty Plus study, a longitudinal South African birth cohort study. The study sample comprised 636 participants with complete data at all relevant time points for the analysis. Household SES and maternal education were measured during pregnancy and the first two years of life, and growth between birth and 4 years of age. Child development was assessed using the Revised Denver Pre-screening Developmental Questionnaire (R-DPDQ). Multivariable regression analyses were used to investigate the association between SES, maternal education, growth and child development, and structural equation modelling was used to analyse the mediation of growth.
Results. In both sexes, higher birthweight and household SES were associated with higher R-DPDQ scores. Increased relative linear growth, particularly between 0 and 2 years, was associated with higher R-DPDQ scores among boys (β=0.82; 95% confidence interval (CI): 0.27 - 1.37) at age 5. Growth status but not SES mediated the association between maternal education and R-DPDQ scores.
Conclusion. Child development at 5 years was independently associated with SES and birthweight. The negative effects of lower maternal education on child development was attenuated by better growth.

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The period from conception to 3 years of age is associated with rapid growth and development. Development during this particularly malleable period lays the foundation for a child's ability to learn, grow and participate in activities with others.[1,2] Children living in impoverished environments are at greater risk of compromised emotional, cognitive and social development.[3] As risk factors are cumulative and interactive,[4] children who experience poor growth early in life are also more likely to be exposed to suboptimal physical and psychosocial environments before and after birth.[5]

Evidence suggests that growth during the early years affects child development outcomes variably in different settings.[6-8] Studies conducted in low-resource settings, such as Colombia and Bangladesh, have explored these relationships in detail, but with conflicting results.[7,8] Differences in findings could be explained by contextual factors, such as variations in extreme (absolute) poverty levels and the prevalence of malnutrition. As there is limited evidence on this in Africa, further research is required to understand the relative effects of individual proximal exposures and the potential additive or mediating effects of growth on child development in low-resource settings.

This study, using data from a longitudinal birth cohort, aimed to explore the relationships between maternal education and household socioeconomic status (SES), early child growth and child development outcomes in a low-resourced, urban setting. The study assessed associations between early childhood growth (between birth and age 4 years) and child development at 5 years of age. It also assessed whether early childhood growth mediated associations between maternal education, household SES and child development at age 5, and if so, how.

Methods

Study design and participants

The analysis used data from the Birth to Twenty Plus (Bt20+) study, a longitudinal birth cohort study of children born in Soweto, Johannesburg, South Africa.[9] For that study, pregnant women attending antenatal care at public health facilities were recruited and 3 273 singletons born between 23 April and 8 June 1990 were enrolled. Details of the study methods, profile and attrition of the Bt20+ cohort are available elsewhere.[9]

Maternal and infant data collected during pregnancy, at birth and between 6 months and 5 years of age were extracted from the Bt20+ database. The analytical sample for the current study included 636 participants with data at all relevant time points.

Child development measure

The Revised Denver Prescreening Developmental Questionnaire (R-DPDQ) was used to assess child development, when the index children were 5 years old.[10] The questionnaire comprises 32 items covering the child's motor, language, personal-social and cognitive abilities, which allows for preschool children at risk of developmental delays to be identified. The assessment included asking caregivers a set of questions, together with children being required to complete a series of age-appropriate tasks. The R-DPDQ was piloted for feasibility and appropriateness prior to inclusion in the Bt20+ study.[11] Internal consistency (Cronbach's alpha) for the R-DPDQ measure in the Bt20+ sample was 0.72. An overall developmental score for each child was derived by adjusting the total raw score for the child's chronological age. The majority of participants had complete data on all 32 items; children with incomplete data missed mostly only one item.[12]

Maternal and household factors

Information on maternal education (years of schooling) and household SES was collected by trained, multilingual interviewers who verbally administered questionnaires to mothers between the third trimester of pregnancy and the first two years of childhood.

Ownership of a number of physical assets (car, television, refrigerator, landline telephone, radio, washing machine and house) was used to derive a proxy measure of household SES at the time. If an asset was present, a score of 1 was assigned; a score of 0 was assigned to assets not present in the household. This approach has been validated in similar studies, including in this cohort.[13,14]

Early childhood growth

In this cohort, weight was measured at birth, and length and height measures were recorded between 3 months and 4 years of age using standard procedures.[15] *Z*-scores were derived using the World Health Organization (WHO) growth standards.[15]

To address collinearity, conditional height variables (subsequently referred to as relative linear growth) were computed as residuals obtained by regressing present height on previous height and weight measures.[16] Conditional growth variables indicate deviation from a child's expected size based on their previous measures relative to the growth of other children (in a population or cohort). A positive value represents linear growth faster than predicted in a specified time interval, whereas a negative value represents slower growth than expected.

For the current analysis, we used relative linear growth between 0 and 2 years, and between 2 and 4 years. These variables are expressed in standard deviation units to allow direct comparison of regression coefficients.

Covariates

Parity, maternal height and quality of child care between 6 months and 2 years (a latent variable combining maternal responsiveness and cognitive stimulation in the home) were included as possible covariates in the regression analyses, based on the literature and prior analyses conducted on this cohort.

Statistical analysis

Our analyses present frequencies and percentages to describe categorical variables and continuous data are summarised using means and standard deviations (SDs). Stata 13.1 (Stata Corp., USA) was used for all analyses and statistical significance was set at $p<0.05$. Differences between the study sample included in the current analysis and the rest of the Bt20+ participants were assessed using Pearson's chi-squared (χ^2) test.

Sex-stratified multiple linear regression models were used to determine the associations between the exposure variables (birthweight and linear growth) and R-DPDQ scores at 5 years, adjusted for maternal education and household SES.

Modelling used a hierarchical approach. Individual factors (i.e. growth variables) were added first (model 1), followed by maternal education (model 2) and then household SES (model 3). Parity, maternal height and quality of child care between 6 months and 2 years (a latent variable combining maternal responsiveness and cognitive stimulation in the home) were included as possible covariates in the regression analyses, based on the literature and prior analyses conducted on this cohort.

Regression analysis was followed by mediation analysis, using structural equation modelling (SEM) to assess whether early-life growth mediated the associations between maternal education, household SES and R-DPDQ scores at age 5. Fig. 1 depicts a standard path diagram for mediation analysis, which has been adapted to our model. A hypothetical SEM model was tested, which was partially informed by the results of the regression and correlation analyses, as well as *a priori* hypotheses as derived from the literature.[7,8] Child sex and quality of childcare in the home between 6 months and 2 years of age were adjusted for use in the SEM model, as these were associated with the outcome in regression analysis.

SEM results decompose the influences of one variable on another into direct, indirect and total effects. Direct effects represent the pathways from exogenous (exposure) variables (maternal education and household SES) to the outcome (R-DPDQ) while controlling for the mediators (birthweight and relative linear growth). Indirect effects depict the pathways from the exogenous variables to the outcome through the mediators. The total effects equal the sum of the direct and indirect (mediation) effects of the exogenous variables on the outcome.[17]

To evaluate the model that best fitted our data, we report goodness-of-fit indices, including the root mean square error of approximation (RMSEA), comparative fit indices (CFI) values and the standardised root mean square residual (SRMR).[17]

Ethical considerations

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand granted ethical approval for the study (ref. no. M120609).

Results

Sample characteristics

The R-DPDQ at age 5 years was completed for 1 231 children in the longitudinal study. Complete data for the questionnaire items and key exposure variables were available for 636 participants. The mean (SD) age of children included in the study at the time of developmental assessment was 62.6 (2.2) months, with 53% being male. Table 1 presents a summary of the study sample characteristics differentiated by sex.

Boys were significantly heavier at birth (mean difference: 110.4 g; 95% confidence interval (CI): 35.8 - 185.0 g). The mean (SD) R-DPDQ score at age 5 years was 44.1 (4.8) (range: 18.1 - 54.5), with boys scoring significantly lower than girls (mean difference: –1.2; 95% CI: –1.9 - –0.4).

The children included in the current analysis were more likely to be Black African, have mothers with comparatively higher levels of education and more household assets, and to score higher on the R-DPDQ ($p<0.05$ for all) compared with those excluded from the analysis. The two groups did not present significantly differently on growth parameters.

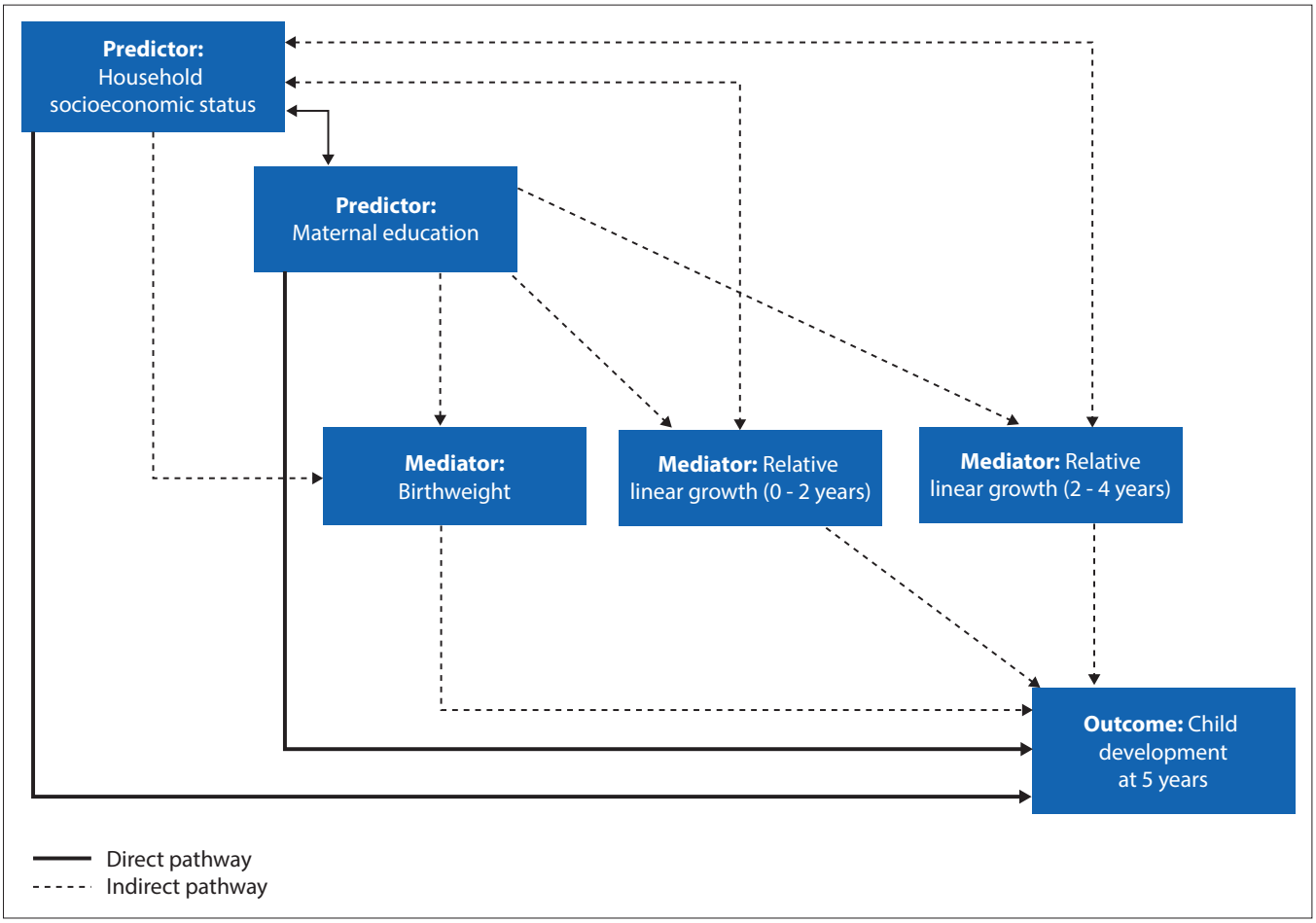

Fig. 1. Path diagram for mediation analysis.

Table 1. Sex-differentiated characteristics of the study sample

Variable	Total (*N*=636)	Boys (*n*=334)	Girls (*n*=302)
Exposure variables			
Maternal education (years), median (IQR)	9 (9 - 11.5)	9 (9 - 11.5)	9 (9 - 11.5)
Household assets (SES score), median (IQR)	4 (3 - 5)	4 (3 - 5)	4 (4 - 5)
Mediator variables (Growth status)			
Birthweight (g), mean (SD)	3 084.89 (480.56)	3 137.47 (485.58)	3 027.08 (469.02)**
Relative linear growth at age 0 - 2 years (*Z*-score), mean (SD)	–0.03 (1.0)	–0.05 (0.9)	–0.01 (1.0)
Relative linear growth at age 2 - 4 years (*Z*-score), mean (SD)	–0.02 (1.0)	–0.01 (1.0)	–0.02 (1.0)
Outcome variable			
R-DPDQ score at age 5 years, mean (SD)	44.1 (4.8)	43.6 (5.3)	44.8 (4.1)**

SES = socioeconomic status; SD = standard deviation; IQR = interquartile range; R-DPDQ = Revised Denver Pre-screening Developmental Questionnaire.
*p<0.05; **p<0.01; ***p<0.001.

Effects of early-life growth and maternal and household exposures on R-DPDQ score at 5 years

In sex-stratified multiple regression analysis, birthweight was positively associated with questionnaire scores for both sexes. These associations remained significant after controlling for maternal education, SES, parity, maternal height and quality of childcare. R-DPDQ scores increased by 0.6 units (β=0.60; 95% CI: 0.12 - 1.09) and 0.5 units (β=0.50; 95% CI: 0.04 - 0.95) for every 1 SD increase in birthweight for boys and girls, respectively (Table 2 and Table 3). In addition, relative linear growth between 0 and 2 years showed an independent association with R-DPDQ scores (β=0.82; 95% CI: 0.27 - 1.37) among boys. Household SES was also independently associated with R-DPDQ scores (for both boys and girls).

Mediation analysis

Correlations among the potential mediators (birthweight, and relative linear growth at 0 - 2 years and at 2 - 4 years), exposures (maternal education and household SES) and the outcome (R-DPDQ score) were examined (Table 4) to inform SEM analysis. Direct, indirect and total effects resulting from the SEM analysis are presented in Table 5.

Household SES showed significant direct effects on R-DPDQ scores, with no evidence of mediation by variables related to early-

Table 2. Sex-stratified regression analysis for the association between early-life growth and R-DPDQ scores for boys

Variables	Model 1 (n=327), β (95% CI)[†]	Model 2 (n=327), β (95% CI)[‡]	Model 3 (n=292), β (95% CI)[§]
Individual factors			
Birthweight	0.76 (0.26 - 1.27)***	0.62 (0.12 - 1.13)*	0.60 (0.12 - 1.09)*
Relative linear growth at age 0 - 2 years	0.87 (0.31 - 1.44)***	0.77 (0.21 - 1.34)**	0.82 (0.27 - 1.37)***
Relative linear growth at age 2 - 4 years	0.73 (0.21 - 1.25)**	0.63 (0.12 - 1.14)*	0.51 (0.01 - 1.02)
Maternal factors			
Maternal education		0.35 (0.15 - 0.55)**	0.19 (–0.02 - 0.40)
Household factors			
Household SES			0.66 (0.29 - 1.04)**
R^2	0.0752	0.1246	0.1512

CI = confidence interval; SES = socioeconomic status.
*p<0.05; **p<0.01; ***p<0.001.
[†]Model 1: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years).
[‡]Model 2: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years), maternal education, maternal height and parity.
[§]Model 3: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years), maternal education, household SES, maternal height, parity and quality of child care between 6 months and 2 years.

Table 3. Sex-stratified regression analysis for the association between early-life growth and R-DPDQ score for girls

Variables	Model 1 (n=289) β (95% CI)[†]	Model 2 (n=285) β (95% CI)[‡]	Model 3 (n=246) β (95% CI)[§]
Individual factors			
Birthweight	0.58 (0.16 - 1.00)**	0.52 (0.12 - 0.92)*	0.50 (0.04 - 0.95)*
Relative linear growth at age 0 - 2 years	0.52 (0.07 - 0.97)*	0.45 (0.01 - 0.89)*	0.26 (–0.22 - 0.74)
Relative linear growth at age 2 - 4 years	0.18 (–0.27 - 0.63)	0.17 (–0.26 - 0.60)	0.10 (–0.36 - 0.55)
Maternal factors			
Maternal education		0.13 (-0.05, 0.31)	0.05 (–0.15 - 0.26)
Household factors			
Household SES			0.45 (0.04 - 0.86)*
R^2	0.0464	0.0745	0.0912

CI = confidence interval; SES = socioeconomic status.
*p<0.05; **p<0.01; ***p<0.001.
[†]Model 1: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years).
[‡]Model 2: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years), maternal education, maternal height and parity.
[§]Model 3: Adjusted for birthweight, relative linear growth (0 - 2 years), relative linear growth (2 - 4 years), maternal education, household SES, maternal height, parity and quality of child care between 6 months and 2 years.

Table 4. Correlations between exposures, outcomes and potential mediators

	Developmental score	Household SES	Maternal education
Predictors			
Household SES	0.2383***	1.00	0.3332***
Maternal education	0.1937***	0.3332***	1.00
Potential mediators			
Birthweight	0.1442***	0.0952*	0.0387
Relative linear growth at age 0 - 2 years	0.1578***	0.1530***	0.0988*
Relative linear growth at age 2 - 4 years	0.1124**	0.0533	0.076

SES = socio-economic status.
*p<0.05; **p<0.01; ***p<0.001.

life growth. Thus, household SES was a key determinant of child development at age 5, independent of birthweight and relative linear growth (either at 0 - 2 years or 2 - 4 years) in this cohort. The direct path for the association between maternal education and R-DPDQ scores was significant and accounted for 78% of the total effect along this pathway. However, the association between maternal education and child development at age 5 was partially mediated by birthweight and relative linear early-life growth (between birth and 4 years) in this cohort. The assessed model indices indicated that the structural equation model fit the data well (Table 5).

Discussion

This study shows that birthweight (for both sexes) and (among boys) linear growth between birth and 2 years of age were positively associated with subsequent child development at age 5. This was independent of maternal education and household SES. The analysis

Table 5. Effects of household socioeconomic status and maternal education on R-DPDQ at age 5 years: Influence of birthweight and relative linear growth in early childhood (n=538)†

Variable	β (95% CI)
Direct effect	
Household SES	0.63 (0.36 - 0.91)***
Maternal education	0.14 (0.00 - 0.27)*
Birthweight	0.53 (0.20 - 0.86)**
Relative linear growth at age 0 - 2 years	0.56 (0.19 - 0.92)**
Relative linear growth 2 - 4 years	0.36 (0.02 - 0.70)*
Indirect effect	
Household SES	0.03 (–0.03 - 0.08)
Maternal education	0.05 (0.02 - 0.08)**
Birthweight	0 (no path)
Relative linear growth at age 0 - 2 years	0 (no path)
Relative linear growth 2 - 4 years	0 (no path)
Total effects	
Household SES	0.66 (0.39 - 0.94)***
Maternal education	0.18 (0.04 - 0.32)*
Birthweight	0.53 (0.20 - 0.86)**
Relative linear growth 0 - 2 years	0.56 (0.19 - 0.92)**
Relative linear growth 2 - 4 years	0.36 (0.02 - 0.70)*

CI = confidence interval; SES = socioeconomic status.
†$\chi2(7)=2.32$; $p=0.940$; comparative fit index = 1.00; root mean square error of approximation = 0.000; standardised root mean square = 0.010; model adjusted for sex and quality of childcare between 6 months and 2 years.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

also showed that the association between maternal education and R-DPDQ scores at 5 years was partially mediated by early-life growth status (birthweight and early-childhood linear growth), but not the association between SES and R-DPDQ scores.

There were clear associations between both prenatal and postnatal growth (using birthweight as a proxy) and child developmental outcomes. Although birthweight is often studied as a dichotomous variable (over or under 2 500 g), using a continuous birthweight measure revealed that higher infant birthweight was associated with higher R-DPDQ scores for both sexes. Positive relationships between birthweight and children's cognitive development have been observed elsewhere, including in lower-resourced settings.[18,19] Thus, interventions aimed at increasing birthweight may support or lead to gains in cognitive development in early childhood, although it is recognised that there is still some uncertainty as to the birthweight range that optimally promotes improved outcomes.[20]

The negative effects of stunting on child development are well described.[1] The pertinent evidence we add is that linear growth, particularly in the first two years of life, had significant independent effects on child development, predominantly among male children in this cohort. These effects persisted even when the influences of maternal and household factors were considered. These findings are biologically plausible as rapid physical growth and brain development generally occurs in the period from conception to age 3 years, providing the foundation for development throughout childhood and later life.[21,22] Well-nourished children will have the essential micro- and macronutrients (i.e. energy, fatty acids and protein) required for brain development and will also be better able to relate with their environment and caregivers and build on their experiences in ways that promote optimal development.[21]

Household SES was independently associated with child development at 5 years of age in both sexes, independent of growth status. Longitudinal studies across income settings describe family income and poverty status as more powerful predictors of children's IQ scores and behavioural development than maternal education, and associate poverty with developmental delays before 1 year of age, with deficits increasing at 5 years of age.[8,23] There is some evidence to suggest that these differences in cognitive performance between SES groups are smaller in more equitable societies.[24]

Maternal education itself has been shown to be a significant determinant of children's cognitive ability, educational performance and subsequent human capital.[1] Previous studies indicate that the effect of maternal education on a child's cognitive and behavioural development remains strong, even after accounting for SES and caregiving effects.[3,25] Although maternal education was positively associated with R-DPDQ scores among male children in this study, the association was attenuated when SES and caregiving effects were controlled for. This suggests that, as shown previously, maternal education may influence child development through other pathways, such as particular parenting characteristics (e.g. caregiver warmth towards the child, maternal sensitivity and responsiveness, or the ability to provide a safe and stimulating environment for the child).[3,8]

This study found that growth between birth and 4 years of age partially mediated the relationship between maternal education (but not SES) and child development scores at 5 years of age. This is the first study in Africa to show this. Two earlier studies in low-income settings examined the extent to which child growth, including linear growth, mediated the effects of SES and maternal education on cognitive development.[7,8] A recent Colombian study found that height-for-age mediated the effect of SES on language development but not the effect of maternal education on cognitive development.[8] In contrast, our findings concur with those from a longitudinal study (using multiple measures of growth), conducted in rural Bangladesh, which showed that growth (particularly in the first two years of life) significantly mediated the association between maternal education and cognitive outcome in children at 5 years of age.[7]

A strength of this study is its use of prospective data from a longitudinal birth cohort in a low-resource setting to test associations,

including biological and environmental factors, at the individual, maternal and household level. Despite the data being from the early 1990s, the availability of sociodemographic information, repeated growth measures and subsequent child development assessments allows this specific research question to be explored in our context.

Study limitations

There are strong reciprocal interactions between cognitive and socio-emotional development, with changes in one potentially contributing to changes in the other.[26] Although the R-DPDQ instrument included some aspects of social and emotional child development, more in-depth exploration is needed of how growth and nutrition could influence behavioural development. The R-DPDQ is a screening tool and thus unable to assess specifics of any particular developmental construct. A useful addition to this study would be to further investigate the effects of social exposures and growth in early childhood on developmental outcomes using more definitive assessment tools. Although we were able to account for a variety of factors in the analysis, we lacked maternal IQ data. This would have strengthened the findings, as maternal IQ is a known moderator of child development.[1] The use of longitudinal data resulted in some participants being lost to inclusion after birth, with some differences noted in the retained sample (as outlined earlier). This reduces generalisability of the results, but, we believe, not in an important way.

Conclusion

Early-life growth appears to affect child development outcomes differently in different settings, which can largely be explained by contextual factors such as poverty and parental education levels.[6-8]

This study provides evidence that early childhood growth (both before and after birth) was positively associated with development scores in children at 5 years of age. Furthermore, it offers encouragement that interventions targeting improved growth in the first few years of life could overcome some of the negative effects of lower maternal education on development outcomes of young children in a limited-resource African setting. Further research is needed to explore the appropriate timing and approach for interventions, such as integrated nutrition and development interventions, to optimise early childhood development outcomes in different contexts.

Declaration. None.

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Author contributions. WS, SN and LR were responsible for study conceptualisation. WS also handled data collection and interpretation, along with SN and JK, and wrote the manuscript. SN, JK, HS and LR contributed to critical review of the manuscript before submission. All authors approved the final manuscript for publication.

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Conflicts of interest. None.

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Is the World Health Organization's multicentre child growth standard an appropriate growth reference for assessing optimal growth of South African mixed-ancestry children?

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In South Africa (SA), it has been estimated that one-third of boys and 25% of girls under the age of 5 years are stunted, according to the World Health Organization (WHO) Multicentre Growth Reference Study. During the past decade, research in developed and developing countries has shown that the international growth standard overestimates stunting and/or wasting when compared with population-specific growth references. Population-specific growth references typically incorporate genetic and environmental factors and can therefore better inform public health by identifying children who may be at risk for malnutrition, or who may be ill. Using the universal growth standard in SA may not be accurately assessing growth. In this article, environmental and genetic factors, and their influence on growth, are reviewed. These points are illustrated through a brief history of the peopling of SA, with an understanding of the socioeconomic and political climate – past and present. We discuss the uniqueness of certain population groups in SA, with contributions regarding some of the shortest peoples in the world and a history of sociopolitical inequities, which may mean that children from certain population groups who are perfectly healthy would underperform using the universal growth standard. Therefore, we suggest that a local population-specific growth reference would serve to better inform public health policies, and address childhood health equity and physical developmental pathways to adult health risk status.

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The World Health Organization (WHO) international growth standard was intended as an indication of how children should be growing under the best possible circumstances, irrespective of genetic influences.[1,2] These circumstances would include: no health, environmental or economic constraints; non-smoking before or after birth; minimum of exclusive 6 months' breastfeeding; term births (≥37 - <42 weeks); and single births.[1] To understand where growth faltering does occur within the growth period, and the explanatory factors that influence the faltering, local research such as that by Norris *et al.*[3] and Schoeman *et al.*[4] is important to understand growth within certain South African (SA) population groups. The current article intends to expand the knowledge base of growth in a different region of SA. The article aims to highlight why there may be plausible reasons (genetic and environmental conditions) to review the WHO growth standard, adopted in SA in 2011,[1] as an appropriate tool to analyse the growth of mixed-ancestry children younger than 5 years in SA. Although many factors influence pre- and postnatal growth, this paper focuses on ancestral genetic influences and environmental living conditions.

Currently, <100 countries worldwide use the WHO Multicentre Growth Reference Study (MGRS), which was developed from longitudinal and cross-sectional data between 1997 and 2003. The aim of the WHO was to provide a universal human growth standard to globally track the general health of children.[2] It was developed using children from six major regions of the world (including the USA, Brazil, Ghana, Oman, India and Norway) to determine whether children grew at the same rate (growth trajectory) under the best possible circumstances (optimal living conditions), irrespective of genetic influences.[2] Although the WHO growth standard is an indication of how children should grow, it is also important to determine how children do grow within a specific set of environmental and genetic influences, i.e. growth reference.[5] It may be the case that many countries, especially developing nations, possibly do not have the necessary resources (money, time, trained personnel) to develop population-specific growth references, and therefore have had to rely on the WHO growth standard.

In 2011, the SA government adopted the MGRS growth standards[1] as part of a new policy called the *Strategic Plan for Maternal, Newborn, Child and Women's Health (MNCWH) and Nutrition in SA 2012 - 2016*.[6] This was to enable fulfilment of some of the key health-related millennium development goals (MDGs),[7] which specifically dealt with health systems, child survival, maternal health, building effective primary health systems and family planning.[7] Therefore, the overarching aim of the 2011 SA policy was to improve primary healthcare for mothers and children, and for the prevention or early diagnosis of diseases/health issues. The revised Road-to-Health Booklet (RtHB) contained the MGRS 2006 growth charts (section D, point 2 of the policy).[6] The RtHB was designed to track the health of mothers and their children more holistically by including all vaccinations, booster

shots, HIV and TB testing, and growth tracing.[6] It also includes advice for primary caregivers regarding breastfeeding practices, maternal interaction with children and milestones for cognitive and motor skills development (National Department of Health, 2012). It was created as an all-inclusive summary of a child's development from birth to 59 months (~5 years).

Although many countries use the MGRS, several studies in India, Peru and Vietnam,[8] the Czech Republic,[9] Central Europe,[10] China[11] and a number of other countries[12] have shown a significant difference in growth patterns of children from birth to 5 years compared with the MGRS growth standard. Studies have demonstrated that population-specific growth references are more accurate measures of growth.[10] Singhal[13] noted that while the prevention of stunting, as well as the promotion of linear growth in small-for-gestational-age or preterm children, has been shown to be beneficial for neurodevelopmental and other health outcomes, the optimal pattern of infant weight gain is likely to differ depending on the population. Natale and Rajagopalan[12] emphasise that otherwise healthy children who do not conform to the MGRS growth standard have a higher probability of misdiagnosis of malnutrition or growth disorders, and their subsequent treatment may lead to an additional burden of disease later in life. Rapid weight gain and postnatal growth acceleration in healthy, full-term infants, often in low- and middle-income country settings, have been associated with a greater risk for obesity and non-communicable diseases later in life.[13] These findings emphasise the importance of applying an appropriate growth reference for infants and children within a specific set of environmental conditions and genetic influences, to mitigate the risks of stunting and obesity.

Therefore, there may be a case for developing population-specific growth charts to better inform SA's healthcare system and policy development, to optimise child health and future preventive healthcare for at-risk populations. In this article, we address whether the MGRS is an appropriate standard for assessing the optimal growth of mixed-ancestry children younger than 5 years in an SA population group. To provide background and context, we begin with a discussion of the impact of genetic and environmental influences on early childhood growth, followed by a discussion of these factors within SA's mixed-ancestry population.

Factors that affect growth: Genetic and environmental influences

Growth is part of human development and is partly defined as the increase of bone size and body mass.[14] It is influenced by various interrelated factors such as genetics[15,16] and the living environment.[17,18] Genetic influences are the causal mechanisms that influence biological growth, resulting in the expression of certain phenotypic traits such as height and weight. These are the result of generations of factors that affect genetic admixture, including sexual selection, gene flow, genetic drift, intergenerational effects and micro-evolutionary adaptations.[14,19] The ancestral influences include micro-evolutionary causal mechanisms and intergenerational effects that may drive differences in height-for-age and weight-to-height-for-age among population groups in various ecogeographical regions of the world. One major mechanism driving body shape was thermoregulation.[20] In warmer climates, humans have adapted a more linear shape that increases the surface area-to-volume ratio, enabling greater heat dissipation compared with those living in colder climates, where the surface area has been reduced and the volume of the thorax increased to assist in heat retention, i.e. Bergmann's rule.[21] This translates to humans having longer limbs (arms and legs) in warmer climates but a stockier body shape (broader chest and shoulders) in colder climates. Another causal mechanism is the amount of exposure to ultraviolet (UV) radiation, which can affect population groups in the same topographical area. For example, within sub-Saharan Africa, the Maasai (Kenya and Tanzania) are among the tallest people in the world, whereas African pygmies (Cameroon, Gabon, Central African Republic, Democratic Republic of Congo, southern Rwanda and Nigeria) are the shortest.[22-25] According to O'dea,[26] the difference in body size between these two groups is most likely due to UV exposure. Both groups have biological adaptations that improved their survival over generations in a unique ecogeographical habitat.[27] If different population groups have significant variation in adult height,[19,21,28,29] there may be a need to further explore growth within an SA context to expand on the research of Norris *et al.*[3] and Schoeman *et al.*[4] Growth deviation among SA mixed-ancestry children from the WHO growth standard could be informative to the health sector if regression analyses of anthropometrical measurements and explanatory variables can highlight why growth deviations exist within an SA context.

In addition to genetic influences, environmental (living) conditions can impact the growth trajectory, including nutritional adequacy,[28,29] hygiene and/or exposure to disease.[30,31] During adverse living conditions, physiological maintenance is more important *in lieu* of growth.[32] Most of our height comes from the growth and development of our skeleton. However, when the primary functions of the body are prioritised to sustain life, skeletal growth is retarded, while the individual survives. While accepting the influence of genetic and intergenerational effects on linear growth, Steckel[33] has described stature as a function of access to resources, and human growth as a net measure of nutrient input (food) v. metabolic output (physical activity and disease). It has been shown that in a hostile (nutrient-deficient, disease-prone and/or high metabolic output) environment, the infancy-childhood transitional age (2 - 3 years) is deferred.[32,34,35] During this transitional change, increased growth hormone insulin-like growth factor 1 (IGF1) is released into the body.[32] This growth-stimulating hormone is known to trigger the activity of osteoblasts (bone) and chondrocytes (cartilage) to promote growth.[36] If living conditions are inadequate, the amount of IGF1 for bone and cartilage growth is reduced, negatively impacting skeletal maturation and consequently height potential. If a child's environmental conditions improve before fusion of the epiphyseal plates of their bones, they may still reach their full height potential.[37] This is known as catch-up growth, when the body accelerates growth and the child's growth trajectory is more rapid than average, making up for loss of linear growth during adverse conditions, and hence returning children to their normal growth curve.[13]

SA and the international growth standard: A case study

We explore the implications for discrepancies between the MGRS growth standard and population- or country-specific growth trajectories, particularly for the mixed-ancestry population in SA. Genetic admixture, in combination with unique sociopolitical and socioeconomic conditions, has created a unique population.[38-40] Together, these factors possibly influence growth rates and development patterns of SA children.

Using the WHO growth standard, ~40% of SA children younger than 5 years of age are stunted.[1] Conversely, the percentage of children classified as overweight in SA was twice the international average (6.1%) for the same age group. The specific concern with the use of the international MGRS in SA is the percentage of children younger than 5 years in the middle- and top-wealth quintiles

(24% and 13%, respectively), who are estimated to be stunted (below the 3rd percentile).[41] The latest SA demographic and health survey based on the MGRS growth standard, reported stunted growth for 1 in 3 boys and 1 in 4 girls.[41] It is doubtful that these children do not have access to adequate nutritional resources to sustain their growth, considering that many of them fall in the middle- and upper-wealth quintiles.[42,43] It is also unlikely that stunting in these children can be attributed to daily living conditions, i.e. disease-prone areas, inadequate sanitation/hygiene or limited access to healthcare. Rather, there might be a predisposition for shorter stature in particular population groups in SA.

In contrast to the stunting phenomenon, SA also has one of the highest obesity prevalences (twice the international average) for children younger than 5 years of age.[41] Is this because children eat poorly balanced meals or have a higher intake of energy-dense, nutrient-poor foods? According to Statistics SA, in 2015 two-thirds of the population lived below the upper-bound poverty line of ZAR992 (USD70) per person per month.[40] With such little purchasing power, most would buy cheaper staple foods such as potatoes, rice, wheat and maize products. Could this impact children's and hence adults' rates of obesity? Is there a correlation between the high percentage of obesity and an international growth standard suggesting children are stunted,[44] i.e. are the caregivers of children who are estimated to be stunted advised to increase the children's daily food intake, thus creating a greater weight-to-height-for-age ratio? To shed light on these matters, it is important to consider factors that influence the growth of children in SA.

According to the government classification system, the people of SA are divided into five population groups, i.e. black, coloured, white, Indian/Asian and other.[45] The original inhabitants of southern Africa were click-speaking foragers, generally known today as San and Khoe.[46] These inhabitants were later joined by the southern migrating agropastoral Bantu-speaking peoples (in reference to the Niger-Kordofanian phylum of African languages) from west and central Africa.[39,40,47] Genetic research shows admixture between these migrants and the people from the Niger-Congo, east Africa, the rainforest pygmies, and finally the San and Khoe in southern Africa.[40] Several different population groups reside in SA, and based on their geographical location, they have diverse genetic contributions from these four main groups. A thousand years later, colonialists from Europe (e.g. Dutch, British, French, German, Spanish) joined the genetic melting pot that forms part of the contemporary population of SA.[48]

With the arrival of Europeans and colonial rule, admixture with the local inhabitants was initially not forbidden. Later, racial segregation was introduced – first socially and then by law under apartheid.[49,50] When racial segregation became law (the Prohibition of Mixed Marriages Act No. 55 of 1949 and the Immorality Act No. 21 of 1950), the descendants from this admixture were known as coloured, a term still used by the democratically elected SA government.[45] For the purposes of this discussion, this population group will be referred to as South Africans of mixed ancestry. This term was decided upon, as their genetic heterogeneity is a more recent (*c.* 360 years) result of admixture.[35,40,49,50] Petersen *et al.*[38] described this population group as having the highest (30%) heterozygosity in the world, with the most diverse genetic admixture between individuals within the same population. They have varied genetic contributions from southern Africa – the indigenous San and Khoe, Bantu-speaking Africans, the colonial descendants and the descendants of slaves and indentured labourers brought to the region.[38,40,49,50] Geographically distinct communities also vary in the percentage contribution from the ancestral genetic input.[38,40] Some individuals sampled by Petersen *et al.*[38] showed ~64% San and/or Khoe genes.

Individuals with a high contribution of indigenous San and/or Khoe genes may be predisposed to shorter stature, as genetically these people have short stature, with men reaching an average adult height of 1.5 m.[51,52] Their linear shape and short stature have been described as biological adaptations to their ecogeographical habitat and food availability.[39,46,52,53] Contemporary San and/or Khoe children have a slow growth period in the first 10 years of their life (40% of adult body size), which is said to be a nutritional adaptation, with a notable adolescent growth spurt.[54] Therefore, their growth trajectory would be expected to differ from the MGRS growth standard. In addition to a genetic predisposition to short stature, many people in SA live in poor socioeconomic conditions. From the mid-19th century to its end, sociopolitical circumstances led to severe socioeconomic inequalities between the SA government's bureaucratically classified population groups. Consequently, many people have been impacted regarding, e.g. quality of education, income prospects, healthcare accessibility, spatial restriction and legalised marital segregation between the population groups (i.e. no admixture).[49] Of the 40% of South Africans who lived below the lower-bound poverty line of ZAR647 per person per month in 2015, 23% were individuals of mixed ancestry.[44]

Urbanisation of people may have increased their accessibility to readily available nutrient-rich food and/or medical facilities, but income levels promoting power-of-purchase have not.[55] Currently, health inequities or disparities are still commonly found among South Africans. This situation is due to social determinants of health, including social, environmental, cultural and physical factors that they are born into, grow up in, and function in throughout their lifetimes.[56,57] In summary, the lack of or limited access to resources may have created an intergenerational effect of shorter stature among certain SA population groups, even if at present the children are reared in better living conditions than in the past.[58]

Conclusion

Many factors that affect growth and the use of growth standards or references may not have been included in this article; however, the overarching aim was to stimulate a discussion pertaining to the WHO standards and its use regarding mixed-ancestry children. The data presented show the diversity of the mixed-ancestry population in SA, and that even a single local growth reference to encompass this broad genetic diversity is unlikely to be effective. Implementation of yet another growth reference will be costly; however, we suggest the need to expand the knowledge base of anthropometric data for different regions in SA in addition to factors that contribute to linear growth, and those that negatively affect it, by conducting further research in other ecogeographical areas, as demonstrated by Norris *et al.*[3] and Schoeman *et al.*[4] Such research can inform the health sector as to why, based on specific explanatory variables, children of mixed ancestry, for example, are under-performing in growth – as the MGRS states. Are these children merely predisposed to a normal shorter stature or is it truly a stunting phenomenon? If the former, using the MGRS growth standard, mixed-ancestry children could possibly have a high probability of being diagnosed as undernourished and their parents may be encouraged to increase their food intake, a factor which may contribute to the high percentage of overweight children and the possibility of an increased burden of disease later in life. Each research puzzle piece regarding children's growth can further assist paediatric clinicians and forensic pathologists with their daily duties. All things considered, these data

show that investigating the optimal growth of SA mixed-ancestry children and understanding population-specific growth references would serve to better inform public health policies to address childhood health equity and developmental pathways to adult health risk status according to the MDGs in Africa.

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Biliary atresia splenic malformation syndrome presenting with hepatic abscesses

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Biliary atresia, a destructive inflammatory cholangiopathy, leads to liver cirrhosis and subsequent death by the age of 2 years if left untreated. Biliary atresia splenic malformation (BASM) syndrome makes up 10% of all cases of biliary atresia. Kasai hepatoportoenterostomy (KPE) may establish continuity of bile flow and slow down progression to cirrhosis if the procedure is performed early in infancy. We describe an 8.5-year-old boy with known BASM syndrome (polysplenia, intestinal malrotation, interrupted inferior vena cava, shortened pancreas, centralised liver and left atrial isomerism) who underwent a successful KPE at the age of 3 months. He presented with features suggestive of a late onset ascending cholangitis (AC) complicated by cholangitic liver abscesses. Resolution of the abscesses with prolonged antibiotic therapy avoided the need for percutaneous drainage. Once the abscesses resolved, the child underwent a successful cadaveric liver transplantation.

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Biliary atresia (BA) is a destructive inflammatory cholangiopathy. It is a heterogeneous disease composed of 3 subgroups: group 1: isolated (perinatal) BA without associated major malformations which is the most common form of the disease (84%); group 2: BA without laterality defects but with at least one major malformation (6%); and group 3: BA occurring in association with one or more laterality malformations (10%) and includes biliary atresia splenic malformation (BASM) syndrome. Groups 2 and 3 have associated anomalies in the cardiovascular and gastrointestinal systems, while genitourinary defects predominate in group 2.[1] Kasai hepatoportoenterostomy (KPE) is a palliative surgical procedure which aims to restore bile flow. Factors determining success of KPE include age, biliary remnant anatomy, extent of liver fibrosis at surgery, number of episodes of ascending cholangitis (AC), subgroup of biliary atresia and surgical expertise.[2] Poor prognosis in BASM syndrome is primarily related to the severity of cardiovascular lesions.[2]

Diagnosis of AC, the most common post KPE complication, requires a high index of suspicion and is considered in the presence of >38.0°C fever with no other focus, increased clinical jaundice and bilirubin levels with acholic stools. Diagnostic confirmation may be obtained by blood cultures and liver specimen culture/histology.[2-5] AC is seen in up to 90% of patients within 1 year of KPE, with episodes beyond 2 years considered uncommon and rarely reported in long-term survivors.[1-4,6] Aetiological agents are intestinal flora pathogens. Empirical treatment with cephalosporins is recommended as causative organisms are identifiable in 30% of cases.[2] Pyogenic liver abscesses of biliary origin are sequelae of acute/repeated/intractable episodes of cholangitis post KPE and are rare.[2,4,6]

The present report aims to educate clinicians on the heterogeneity of BA and alert them to complications that may occur after a successful KPE. Ethics permission was obtained from the University of the Witwatersrand's Human Research Committee (ref. no. M200383). Permissions were also obtained from the head of the Department of Paediatrics and the CEO of Chris Hani Baragwanath Academic Hospital.

Case

The patient was an 8.5-year-old male with BASM syndrome who underwent a KPE and Ladd's procedure for BA and intestinal malrotation at the age of 98 days. The KPE was successful and the child remained anicteric with pigmented stools until the age of 6 years. Progression to cirrhosis and portal hypertension was noted over the following 2 years. At the age of 8.5 years he was admitted with fever. On examination, he was drowsy, pyrexial (38.5°C), jaundiced, clubbed, and pale, and his oxygen saturation was normal. Abdominal examination revealed a right hypochondrial surgical scar, ascites, a hard nodular non-tender 6 cm hepatomegaly, a palpable (unusual in BASM) 6cm firm splenomegaly and pale stool on rectal examination. Neurological examination revealed a child with confusion and incoherent speech.

Laboratory investigations were documented as follows: haemoglobin 13 g/dL; platelet count 78 $\times 10^9$ L; white cell count 28.42 $\times 10^9$ g/L (80% neutrophilia); and C-reactive protein (CRP) 131 mg/L. His liver function tests revealed the following: total bilirubin 201 µmol/L (previously 82 µmol/L); conjugated bilirubin 183 µmol/L; total protein 51 g/L; albumin 18 g/L; alanine transaminase 539 U/L; aspartate transaminase 933 U/L; alkaline phosphatase 612 U/L; γ-glutamyl transferase 69 U/L; international normalised ration (INR) 1.97; and normal α-fetoprotein levels. Ammonia was persistently high at 200 µmol/L. His blood, urine, ascitic and stool cultures remained negative. Ascending cholangitis was suspected and managed with intravenous cefotaxime. Chronic encephalopathy, worsened by cholangitis, was managed with anti-liver-failure therapy and ascites were managed with albumin infusions and diuretics. Fever persisted and tazobactam and amikacin were introduced for suspected nosocomial sepsis.

A hepatic ultrasound identified an abscess measuring 60 mm × 64 mm in the right lobe. Repeat ultrasound within a week revealed

multiple liver abscesses. (Fig 1A) Computed tomography (CT) of the abdomen confirmed the presence of a larger hepatic abscess associated with smaller cholangitic abscesses and documented features in keeping with BASM syndrome (polysplenia, midline liver, azygous continuation of the inferior vena cava, short pancreas and mainly right-sided small bowel) (Fig 1B). Echocardiography revealed left atrial isomerism and confirmed interruption of the inferior vena cava with azygous continuation to the superior vena cava.

A pigtail insertion for drainage of the larger hepatic abscesses was planned. In view of underlying encephalopathy, significant ascites and clotting abnormalities, the patient was deemed too unstable for percutaneous/surgical drainage and was managed medically. Due to fever persistence, antibiotics were changed to meropenem and metronidazole. Serial ultrasounds confirmed gradual resolution of the hepatic abscesses within 3 weeks of diagnosis (Fig 1A). Although the patient's fever resolved and his mental state improved, he remained jaundiced. He was discharged 6 weeks after admission, on completion of 33 days of meropenem and 14 days of metronidazole. He was maintained on amoxicillin/clavulanic acid for AC prophylaxis. Repeat ultrasound one month after discharge showed no evidence of hepatic abscesses. During the following month, the child underwent a successful cadaveric liver transplantation. Liver explant histology confirmed cirrhosis and presence of occasional bile lakes with no abscesses.

Discussion

The aetiological heterogeneity of BA alerts medical professionals to evaluate patients for associated abnormalities. [1,2] In BASM syndrome these abnormalities can include polysplenia (77%), asplenia (11%) situs inversus abdominis (37%), intestinal malrotation/atresias, left-sided/central liver and annular pancreas or an absent pancreatic tail. Vascular anomalies commonly involve the portal vein (61%) and inferior vena cava (absence in 39% of cases). Cardiac anomalies can include dextrocardia and tetralogy of Fallot.[1,2] Most children with BA ultimately require liver transplantation, with KPE remaining the preferred initial procedure of choice.[3,6] Proper evaluation for BASM syndrome allows adequate pre- and postoperative surgical planning for KPE and liver transplantation to ensure similar outcomes to isolated BA.[2] However, the severity of the cardiac defects often determines KPE outcomes and influences the decision regarding referral for liver transplantation.[2]

Prevention of AC with a long Roux-en-Y loop, routine use of postoperative steroids, prolonged antibiotic prophylaxis, a high index of suspicion for the diagnosis irrespective of the patient's age and appropriate duration of antibiotic treatment of acute episodes may improve native liver survival and delay the need for transplantation. [2,5] Treatment of AC can be escalated from cefotaxime to piperacillin-tazobactam and then meropenem if there is no clinical improvement. Ceftriaxone is avoided, as it may lead to bile sludging. Antifungals may be considered.[2,5] Complicated or intractable episodes of cholangitis are considered transplant indicators, with the number of cholangitic episodes being prognostic markers of liver transplantation, reflecting fibrosis progression.[3,5] Prevention is especially relevant in low-income countries where transplantation may not be feasible owing to limited resources and lack of accessibility to liver transplant programmes. Common practice includes cyclical use of prophylactic antibiotics

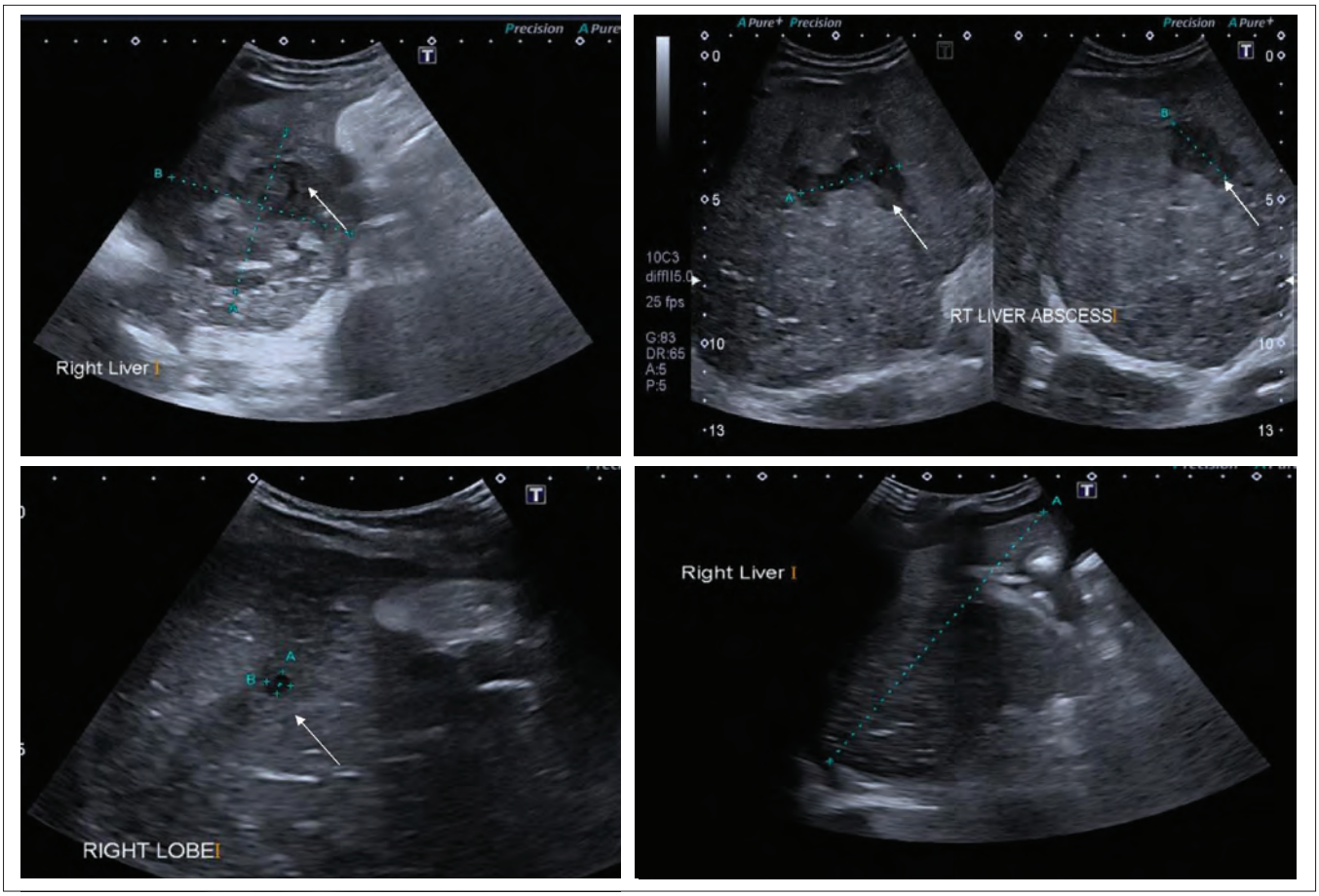

Fig. 1A. Abdominal ultrasound: Progression of the hepatic abscess (white arrow) (i) *initial (60 mm x 64 mm),* (ii) *3 weeks later (39 mm × 28 mm),* (iii) *1.5 months later (4.8 mm × 4.9 mm) and complete resolution* (iv) *3 month later.*

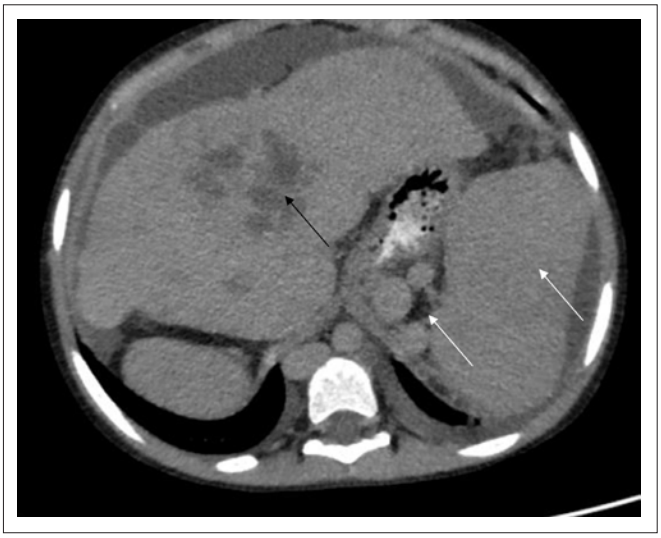

Fig. 1B. CT Abdomen indicating polysplenia (white arrows) and a midline liver with an abscess (black arrow).

(amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, ciprofloxacin) but concerns for drug resistance and contradictory preventative results require more prospective studies.[2,5]

Awareness of AC complications encourages earlier radiological investigations to exclude cholangitic abscesses. Causative organisms include *Escherichia coli* (21 - 36%), *Enterobacteriaceae* and polymicrobial infections.[5] Antibiotics (cefotaxime or piperacillin-tazobactam) are generally parenterally administered for 4 - 6 weeks, with antibiotic choice guided by antimicrobial sensitivity tests.[5] When signs of infection persist, indications for percutaneous drainage or surgical intervention need to be assessed.[2] Hepatic abscesses have been documented as post KPE complications in 3.6% (n=1/28) of cases.[6] On pus culture, two reported cases of cholangitic abscesses post KPE revealed a polymicrobial infection in one case and *Klebsiella* spp. in the other.[4]

Conclusion

We were unable to compare our patient management and outcomes with published reports owing to the rarity of the condition and unconfirmed microbial cause. In the era of liver transplantation, hepatic abscesses remain rare in high-income countries. In low-income countries, individualised therapy of cholangitic abscesses can yield a good outcome, occasionally bridging time to liver transplantation.

Declaration. None.

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Neonatal medium-sized vessel vasculitis: A rare case report

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Vasculitis is a rare disorder during the neonatal period. We present a term male neonate of consanguineous parents and birthweight of 4 030 g who presented at 11 days of life with an evolving skin rash. There was no history of drug exposure in the neonate except for routine care. On day 7 of life, multiple erythematous plaques with necrotic or pustular centres appeared. There were no signs of mucosal involvement or sepsis and laboratory findings were normal. Skin biopsy revealed small and intermediate vessel vasculitis. At follow-up 2 weeks after discharge from the hospital, the skin lesions persisted, and at age 2 months, the patient presented with features of severe pneumonia and subsequently died. Vasculitis was reported as the cause of death on postmortem biopsy.
Keywords. neonate; vasculitis; cellulitis; acute oedema of infancy.

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Inflammation of the skin and soft tissues is uncommon in healthy neonates, but when it occurs it should primarily be considered as being due to infective or inflammatory processes, most commonly cellulitis. Organisms commonly implicated in neonatal cellulitis include group B *Streptococcus* (GBS), *Staphylococcus aureus*, Gram-negative bacteria, anaerobic microorganisms and fungi. In primary neonatal cellulitis, the infection is acquired from the mother during the intrauterine period or during the passage from the vaginal canal, or postnatally from environmental sources. In secondary skin infections, haematogenous spread of microorganisms to the skin occurs during systemic infection, i.e. neonatal sepsis.[1,2] Clinical symptoms of infection such as fever, poor feeding, lethargy, irritability, respiratory distress, vomiting and gastrointestinal problems, along with skin manifestations, support infection as a potential cause of disease. Drug reactions, although uncommon, may cause skin eruptions in the neonatal period.[3,4]

Skin eruptions may be a symptom of systemic disorders other than infections, and may be prominent in patients with vasculitis disorders.

Vasculitis is defined as inflammation of the wall of blood vessels.[5] Its aetiology is not fully understood but during pregnancy the immune system undergoes many changes to accommodate the fetus. Known causes of vasculitis include the following: infections (hepatitis B and *Streptococcus* spp.); other autoimmune diseases (lupus and scleroderma); and malignancies (leukaemia and lymphoma).[5] The treatment of vasculitis in infants is not defined and recommendations are based on generalisations from large observational cohort studies in adults. The overall goal of treatment is control of vessel inflammation and prevention of irreversible vascular and organ damage. Corticosteroids are the first-line therapy; however, half of affected children need an additional immunosuppressant. Additionally, intravenous immunoglobulin (IVIG; 2 g/kg) and aspirin should be administered within 10 days of fever onset.[8-11]

The classification and severity of disease are determined based on the size and site of involved vessels, underlying pathophysiology and the extent of vascular injury.[6] Takayasu's arteritis is an example of a large-vessel vasculitis in childhood, whereas Kawasaki disease and polyarteritis nodosa are examples of medium-vessel vasculitis disorders. Henoch-Schönlein purpura is a vasculitic process involving small vessels. The neonatal period is an uncommon time for the presentation of vasculitis and primary neonatal vasculitis is a particularly rare entity.[7]

We report a rare case of neonatal vasculitis presenting with skin manifestations similar to infection-based cellulitis.

Case report

An 11-day-old term male neonate with a birthweight of 4 030 g was delivered by caesarean section from a healthy mother after a normal pregnancy (gravida 1, para 1 miscarriages 0). From the third trimester, the mother received levothyroxine (50 µg daily) to treat primary hypothyroidism. There was parental consanguinity, with no specific family history of vasculitis. There was no history of significant medical problems or drug exposure in the parents. There was no history of drug exposure in the neonate except vaccination with oral poliovirus vaccine, bacille Calmette-Guérin (BCG) and hepatitis B vaccine, and oral vitamin D drops for the first 5 days of life in accordance with routine care in Iran. He was circumcised on the fifth day of life with lidocaine as a local anaesthetic. The patient was breastfed. There were no concurrent symptoms of sepsis such as fever, irritability, poor feeding, lethargy, vomiting, diarrhoea, respiratory distress, or other problems in neonates.

After the appearance of skin lesions, the patient was admitted to a paediatric hospital in his hometown (Qom, Iran) for sepsis work-

up and antibiotic treatment. Owing to the lack of improvement, he was referred to our hospital.

From day 7 of life, a disseminated skin rash manifesting as large, targetoid erythematous patches was noted. There were purpuric plaques on the face, trunk, limbs and digits. The proximal, middle and distal phalanges of the middle fingers of both hands were involved. Fig. 1 illustrates the skin lesions. There were no concurrent symptoms of sepsis and no sign of mucosal involvement. The vital signs of the neonate were normal as follows: axillary temperature, 37.2°C; pulse rate, 110 bpm, respiratory rate, 38 bpm; oxygen saturation on room air, 95%. On further examination, he had a mild hydrocele.

He commenced intravenous antibiotic therapy with vancomycin and gentamycin to cover common skin infections, i.e. infection with *Staphylococcus* spp., group B *Streptococcus* spp. and Gram-negative bacteria. Antibiotics were administered after culture results were obtained. The white blood cell count (WBC) was 9.7 × 10^9/L, with 34% polymorphonuclear cells and 56% lymphocytes. The neonate's haemoglobin level was 14 g/dL, and platelets were 301 000/µL. C-reactive protein (CRP), blood urea nitrogen (BUN) and creatinine levels were normal, and blood, skin lesion, cerebrospinal fluid (CSF) and urine cultures were negative for bacteria.

Owing to the lack of improvement of the skin lesions despite antibiotic administration, and after consultation with a dermatologist, a differential diagnosis of acute haemorrhagic oedema of infancy or erythema multiforme was considered, and a skin biopsy was done. Histology confirmed the presence of small and medium-sized vessel vasculitis (Fig. 2). The histological findings were notable in terms of the dense perivascular inflammation in the dermis and subcutaneous tissue, small vessel damage with swelling of endothelial cells, fibrinoid necrosis of the vessel wall, leukocytoclasis and intramural thrombus (arrows in Fig. 2). The perivascular inflammatory infiltrate consisted of neutrophils, lymphocytes and a few eosinophils.

Based on transition course of disease, the consulting dermatologist recommended ongoing immunodeficiency evaluations, as well as conservative supportive care. As the overall condition of the neonate was normal, his parents decided to discharge against medical advice for the provision of continuous evaluations and management of the patient. The patient was discharged in a stable condition with the written consent of the parents and an outpatient work-up for inherited immunological or rheumatological conditions was planned. The autoimmune disease work-up and vasculitis evaluations of both parents were also requested after discharge.

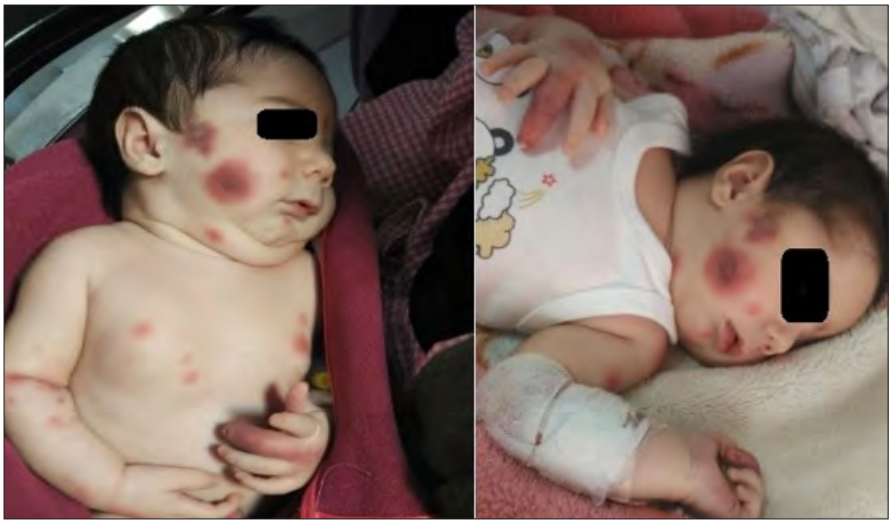

Fig. 1. Skin eruptions on the face and right hand of the neonate.

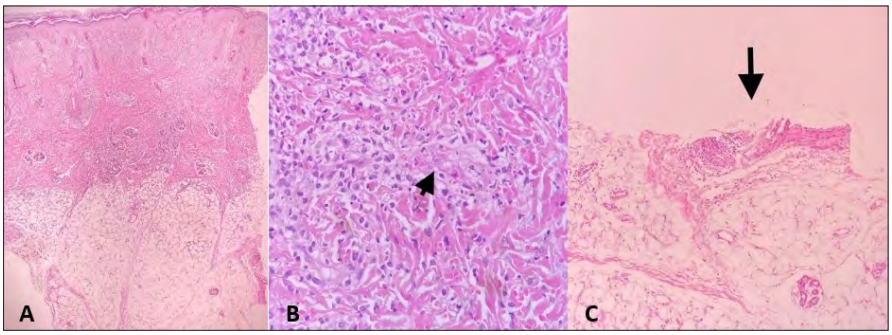

Fig. 2. (A) Histopathological examination revealed dense perivascular inflammation in the dermis and subcutaneous tissue (H&E; 40×). (B) Small-vessel damage with swelling of endothelial cells, fibrinoid necrosis of vessel wall, leukocytoclasis and intraluminal thrombus were observed (arrow). Perivascular inflammation consists of neutrophils, lymphocytes and a few eosinophils (H&E; 40×). (C) A medium-sized subcutaneous vessel (arrow) also revealed dense perivascular infiltration of neutrophils and lymphocytes and leukocytoclasis (H&E; 40×).

At subsequent follow-up, the skin lesions persisted. In the autumn of 2019, early in the influenza season, the patient died with fulminant respiratory disease (rapidly progressing over 4 - 5 hours) that was non-responsive to medical intervention. He was 2 months old at the time of death. No aetiological agent was identified in the terminal disease episode. A postmortem examination revealed vasculitis as the cause of death.

Discussion

This case was notable for the early onset of idiopathic histologically confirmed vasculitis involving small- and medium-sized blood vessels, and a rapidly fatal course. Vasculitis is an unusual disorder in the neonatal period. Transplacental passage of maternal protein may lead to a transient vasculitis in infants born to mothers with underlying disorders such as Behçet disease, Sjögren's syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease, or microscopic polyarteritis.[12-15]

Although Kawasaki disease is a relatively common form of vasculitis in children, it is rarely reported in neonates.[16] Infantile Henoch-Schönlein purpura, or acute haemorrhagic oedema of infancy (AHEI), is a self-limiting cutaneous vasculitis of small vessels without any systemic involvement that occasionally presents at birth.[12]

AHEI manifests with fever, oedema and large palpable purpuric skin lesions that resemble those seen in Henoch-Schönlein purpura. Conservative management is the most commonly adopted approach in

treating AHEI. The skin manifestations of our patient were similar to those observed in AHEI; however, fever and oedema were not significant. The persistence of the skin manifestations and outcome of our patient do not support a diagnosis of AHEI.

In a report by Roy *et al.*,[16] an 8-month-old male infant presented with skin eruptions which developed following a mild respiratory illness for which amoxicillin-clavulanate and paracetamol were prescribed. The rash consisted of multiple plaques and oval-to-round ecchymotic patches varying in diameter from 2 to 5 cm, involving the arms, hands, face, gluteal area, feet and legs. No histological assessment was done in the diagnostic work-up of the case. Topical application of calamine lotion resulted in resolution of the skin rash.

Allergic reactions to drug administration often involve the skin.[17] In view of the low prevalence of allergy in the neonatal period,[18] and the negative history of drug exposure in our patient, this diagnosis would have been highly unlikely. Malignancies, including lymphoma and other lymphoproliferative syndromes, may result in secondary vasculitis and in cases of persistent vasculitis,[19] malignancy should be considered. Altammar and Lang[20] reported a case of Kawasaki disease in a 15-day-old male who presented with irritability, a rash and poor feeding. Fever (39.6°C), tachypnoea, tachycardia, extreme irritability and a generalised maculopapular rash were noted on physical examination. Bilateral non-purulent conjunctivitis, bilateral non-pitting oedema, palmar erythema, erythema of the feet and arthritis were present on day 6 of hospitalisation. The complete blood count, CRP, and erythrocyte sedimentation rate (ESR) were normal at baseline, but thrombocytosis was detected on day 9 of hospitalisation. Symptoms of the disease resolved subsequent to intravenous immunoglobulin administration. Coronary artery aneurysms were not detected in the echocardiography.[20]

Krapf *et al.*[21] reported a neonate with fatal myocardial infarction owing to vasculitis of the coronary arteries. Pathological involvement of the coronary arteries is indistinguishable from mucocutaneous lymph node syndrome and/or infantile periarteritis nodosa. The epidemiology and etiology of these rare conditions remain to be clarified.[21]

In a case report by Simonetti *et al.*,[22] a term neonate with aesophageal atresia requiring surgery on day 2 of life developed respiratory distress, empyema, thrombocytopenia, severe proteinuria, and haematuria with red cell casts on urinalysis, a rise in creatinine level, and a generalized maculopapular rash. Leukocytoclastic vasculitis with marked eosinophilia was detected in the skin biopsy. A 7-day course of intravenous methylprednisolone cured the patient's renal involvement and at long-term follow-up (12 months old) the patient was well.[22]

Primary or secondary vasculitis in the neonatal period can be life-threatening and requires timely diagnosis and treatment. The death of our patient during the early period of seasonal influenza led us to consider that a fulminant viral infection may have contributed to his death. As he died prior to widespread circulation of SARS-CoV-2, his death was not considered to be COVID-19 related. It is a pity that specific viral diagnostic tests were not done in our patient during his terminal admission episode.

Conclusion

Neonatal vasculitis should be considered in infants under 28 days of life who present with the following: widespread skin involvement resembling cellulitis; no concurrent signs and symptoms of sepsis; and no resolution despite antibiotic administration. Timely work-up and laboratory assessment must be done for the initiation of appropriate treatment, and to prevent death in early infancy. Also, we conclude that the parents need to be investigated for an autoimmune disease.

Declaration. Written informed consent was obtained from the parents of the patient to publish this information and the images of the neonate.

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Author contributions. MF and FA: study design; MF, FA, and SS: manuscript preparation; ST and ST: critical review.

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CPD June 2022

The CPD programme for *SAJCH* is administered by Medical Practice Consulting.
CPD questionnaires must be completed online at www.mpconsulting.co.za

South Africa regains polio-free status: Processes involved and lessons learnt

1. Lessons learnt from this experience include:
a. reaffirming the importance of continued commitment to polio eradication efforts
b. strengthening health systems through quality improvement projects
c. ensuring accountability in supervision
d. monitoring of polio-related indicators.

Regarding neonatal medium-sized vessel vasculitis

2. Which of the following statements are true?
a. Inflammation of the skin and soft tissues is uncommon in healthy neonates.
b. The classification and severity of vasculitis is determined based on the size and site of involved vessels.
c. Allergic reactions to drug administration often involve the skin.
d. Primary or secondary vasculitis in the neonatal period is not life-threatening.

Regarding paediatric gastrointestinal endoscopy

3. The most common presenting symptoms in children undergoing gastroscopy include
a. patients evaluated for PEG insertion for feeding due to feeding difficulty
b. poor weight gain/failure to thrive
c. chronic abdominal pain
d. chronic diarrhoea.

Regarding male partners' experiences of early pregnancy ultrasound scans in Soweto, South Africa

4. Which of the following statements are true:
a. Partners and fathers can promote maternal health and wellbeing by encouraging positive behaviours.
b. Men face a range of barriers in low- and middle-income settings.
c. Cultural beliefs and practices do not influence father involvement.
d. Routine health checks provide important opportunities to involve male partners and raise awareness of the importance of their involvement in their child's development.

Regarding training, confidence and knowledge of healthcare workers with regard to HIV and infant feeding

5. Which of the following statements are true:
a. Breastfeeding is always encouraged even for mothers living with HIV.
b. There is a low risk of HIV transmission from mother to child through breastmilk.
c. This study shows that the majority of healthcare workers were insufficiently trained in the HIV component of this policy.
d. Treatment failure can only be diagnosed in patients who are compliant with their ART.

Regarding moderate to severe neonatal encephalopathy with suspected hypoxic-ischaemic encephalopathy in cooled term infants born in Tygerberg Academic Hospital

6. Which of the following statement are true?
a. The bed occupancy rate for the labour ward was 52% during the study period.
b. The longest waiting time for theatre was 5 hours.
c. All the women in the study were referred for specialist care during the antenatal or intrapartum period.
d. Nine vacuum-assisted delivers were done for poor progress in the second stage of labour.

Regarding primary hyperoxaluria

7. The diagnostic work-up includes:
a. a 24-hour urine or spot urine analysis for oxalate crystals
b. histology
c. imaging
d. routine health checks provide important opportunities to involve genetic mutation analysis.

Regarding infant injuries treated at Red Cross War Memorial Children's Hospital, Cape Town, South Africa

8. The most common type of
a. falls was from the bed
b. burn was from hot water
c. transport-related injury was motor vehicle crashes
d. other injury was due to being struck.

Regarding the trajectory of general movements from birth until 12 - 14 weeks corrected age in very low-birthweight and extremely low-birthweight infants born preterm

9. The multivariate analysis included the following variables:
a. higher birthweight
b. lower birthweight
c. gestational age at birth
d. intraventricular haemorrhage grade III.

Regarding anaemia, iron and vitamin A status among South African school-aged children living with and without HIV

10. True or false?
No differences in anaemia, iron-deficient erythropoiesis and iron deficiency anaemia were found between HIV+ than HIV– children.

Regarding child development at age 5 years

11. True or false?
Child development at 5 years was independently associated with SES and birthweight.

A maximum of 3 CEUs will be awarded per correctly completed test.
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SAPA WEBINAR SERIES

Join us on the last Wednesday of each month at 5pm, for up-to-date information on important paediatric topics. Presenters are paediatric experts from all over South Africa. You can engage with them and have your pressing questions answered!

Webinars are also recorded (unless there is content the speaker cannot make publicly available) and available on the SAPA YouTube channel for viewing, at your convenience. SAPA members earn 1 CPD point per webinar for attendance.

In recent months we have discussed the effect of the common respiratory pathogens on our patients, climate change, as well as delved deeper into the intricacies of adolescent medicine. We truly enjoy challenging the depth and breadth of our knowledge with these webinars. If you haven't joined one yet, go to **paediatrics.org.za** for details on how to register.

INFECTIOUS DISEASE WORKSHOP HIGHLIGHTS

SAPA and SASPID hosted a workshop on paediatric infectious diseases in July 2022.

While the world of paediatric HIV and TB is rapidly changing, and keeping up with the latest can be tricky, South African paediatric ID specialists provided bite-sized chunks on new treatment regimens, and how to use them. Attendees received updates on rabies, congenital syphilis (you're not alone if you don't have Penicillin available at your hospital!), tetanus and hepatitis, and also learnt why 'TORCH' is out of date.

SAPA members can access this workshop recordings by logging in to the SAPA website: **paediatrics.org.za**

GROUP B STREPTOCOCCUS AWARENESS

Group B Strep Support Group of South Africa was started by a team of passionate health care professionals with the hopes of improving the awareness and treatment of all those affected, directly or indirectly, by Group B Streptococcus (*Streptococcus Agalactiae*).

While still in very early stages, they have set an ambitious plan to grow their social media presence and create support groups for both parents and patients, affected by GBS. Social media is used to share material relevant to both healthcare workers and parents – aiming to improve awareness around prevention, diagnosis and treatment of GBS. They also have a support group/network for parents or patients affected by GBS to connect.

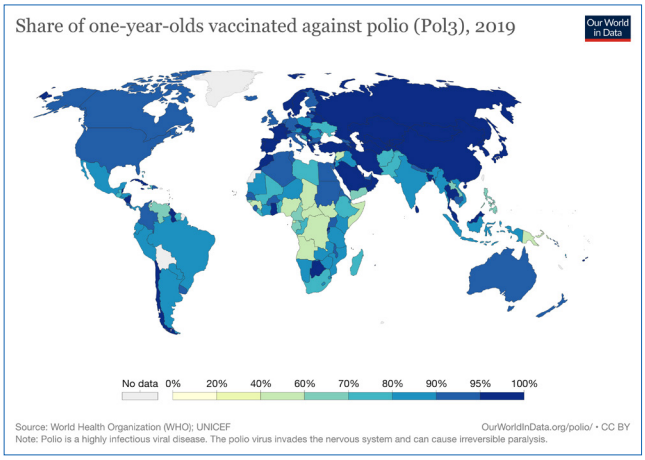
You can find them on Instagram (**@gbssupportsa**) or Facebook (Group B Strep Support Group SA). Alternatively, Whatsapp "Hi" to the Group B Strep Support Group SA Hotline +27 72 907 1622, or email your name and contact details to **groupbstrepsa@gmail.com** to find out more, and how you can get involved in this exciting project.

TEACHING? REVISING THE BASICS? CHECK OUT PEDS CASES

In addition to practicing as clinicians, many of us have the opportunity to share our knowledge of how to care for children with our junior colleagues and medical students. A valuable resource is **Peds Cases**, a repository of podcasts, short notes, cases and videos on common paediatric problems. The content is aimed at the undergraduate level and succinctly conveys key learning points that will help our students grasp the concepts they need in the field of paediatrics. This resource can be used to plan teaching, design assessments or simply share with students to aid learning.

POLIOVIRUS ERADICATION – WHERE ARE WE NOW?

Polio eradication has been a global priority since 1988, with a 99,9% reduction in cases to date. South Africa's polio-free status was withdrawn in 2017 due to a decline in poliovirus immunisation coverage and inadequate surveillance of acute flaccid paralysis cases. With a recent case of wild type poliovirus in Malawi and increasing concern regarding circulating vaccine-derived poliovirus, efforts in polio eradication have had to be revisited. Learn more about the Global Polio Eradication Initiative (GPEI) strategies for eradication of wild type poliovirus, including the innovations in poliovirus immunisations, **here**. For additional data on polio with amazing interactive graphics (such as the share on one-year-olds vaccinated against polio, pictured below) visit **Our World in Data.**



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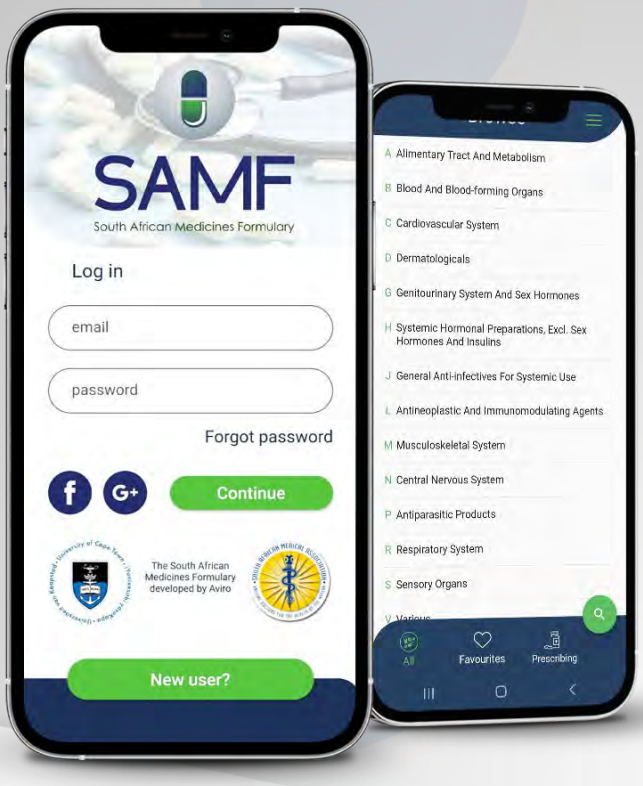

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