Pediatric Acute Respiratory Distress Syndrome in South African PICUs: A Multisite Point-Prevalence Study

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OBJECTIVES: To describe the prevalence of pediatric acute respiratory distress syndrome (pARDS) and the characteristics of children with pARDS in South African PICUs.

DESIGN: Observational multicenter, cross-sectional point-prevalence study.

SETTING: Eight PICUs in four South African provinces.

PATIENTS: All children beyond the neonatal period and under 18 years of age admitted to participating PICUs.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Clinical and demographic data were prospectively collected on a single day of each month, from February to July 2022, using a centralized database. Cases with or at risk of pARDS were identified using the 2015 Pediatric Acute Lung Injury Consensus Conference criteria. Prevalence was calculated as the number of children meeting pARDS criteria/the total number of children admitted to PICU at the same time points. Three hundred ten patients were present in the PICU on study days: 166 (53.5%) male, median (interquartile range [IQR]) age 9.8 (3.1–32.9) months, and 195 (62.9%) invasively mechanically ventilated. Seventy-one (22.9%) patients were classified as being "at risk" of pARDS and 95 patients (prevalence 30.6%; 95% CI, 24.7–37.5%) fulfilled pARDS case criteria, with severity classified as mild (58.2%), moderate (25.3%), and severe (17.6%). Median (IQR) admission Pediatric Index of Mortality 3 risk of mortality in patients with and without pARDS was 5.6 (3.4–12.1) % versus 3.9 (1.0–8.2) % ($p = 0.002$). Diagnostic categories differed between pARDS and non-pARDS groups ($p = 0.002$), with no difference in age, sex, or presence of comorbidities. On multivariable logistic regression, increasing admission risk of mortality (adjusted odds ratio [aOR] 1.02; 95% CI, 1.00–1.04; $p = 0.04$) and being admitted with a respiratory condition (aOR 2.64; 95% CI, 1.27–5.48; $p = 0.01$) were independently associated with an increased likelihood of having pARDS.

CONCLUSIONS: The 30.6% prevalence of pARDS in South Africa is substantially higher than reports from other sociogeographical regions, highlighting the need for further research in this setting.

KEY WORDS: low middle-income country; pediatric acute respiratory distress syndrome; pediatric intensive care units; prevalence

It has been estimated that between 1% and 10% of children admitted to PICU develop pediatric acute respiratory distress syndrome (pARDS) (1), with high associated mortality and both short- and long-term morbidity (2–5). The multisite Pediatric Acute Respiratory Distress Incidence and Epidemiology (PARDIE) study reported that 3% of patients being treated in the PICU presented with or developed pARDS (5); however, most study sites were

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RESEARCH IN CONTEXT

- Acute respiratory distress syndrome (ARDS) is a clinical syndrome caused by direct (e.g., pneumonia) or indirect pulmonary damage (e.g., from sepsis). It is characterized by acute, widespread inflammation, alveolar damage, and lung capillary endothelial injury with associated hypoxemia.
- Resource-constrained environments may have a high burden of pediatric ARDS (pARDS) possibly owing to socio-economic determinants of poor health, but this has not been sufficiently studied.
- This report presents the findings of the first multicenter pARDS prevalence study in South Africa, a middle-income country with substantial poverty and associated burden of pediatric disease.

in well-resourced countries, with no representation from Africa. Being from a middle-income country was independently associated with increased mortality in children with pARDS (5). The Second Pediatric Acute Lung Injury Consensus Conference (PALICC2) recently highlighted the paucity of data related to pARDS from resource-constrained regions, where the high burden of childhood disease and comorbidities may place children at increased risk of pARDS and poor outcomes (6, 7). The burden and epidemiology of pARDS in critically ill children admitted to PICU in low-income and middle-income countries are not clear (7).

A recent single-center study from South Africa, a middle-income country with high rates of poverty and inequality, reported an extremely high prevalence of pARDS of 30.3% (8). This study was; however, conducted during the second wave of the COVID-19 pandemic, with associated restrictions including cancelation of elective surgeries and other clinical services, and it is unclear if the findings could be generalized to usual circumstances after the lifting of COVID-19-related restrictions and/or whether the results were generalizable to other PICUs in South Africa. This study aimed to describe the prevalence and clinical profile of children with pARDS, admitted to multiple PICUs within different regions of South Africa, using the 2015 PALICC diagnostic criteria (5) and after the relaxation of COVID-19 restrictions.

MATERIALS AND METHODS

Researchers from eight study sites in four of the nine South African provinces volunteered to provide data for this study after a call for participation was made through an informal collegial network. Institutional research ethics committee (REC) approval was obtained from all study sites (University of the Free State—UFS-HSD2021/0925/2501; University of Cape Town—HREC Ref 507/2021; KwaZulu-Natal—BREC Ref RECIP011/2021; Stellenbosch University—N21/10/103_RECIP_UCT_507/2021; University of the Witwatersrand—M210658) and the need for full written parental informed consent was waived for all but the two University of the Free State study sites (Pelonomi and Universitas hospitals), where informed consent was obtained from each patients' parents or legal guardian. This study adhered to the principles outlined in the Declaration of Helsinki (most recently amended in 2013) (9) and the South African Department of Health's research ethics guidelines (10).

This was a descriptive, cross-sectional, multicenter point-prevalence study of all infants and children under 18 years of age, admitted to PICUs at each of the eight participating sites (**e-Appendix 1**, http://links.lww.com/PCC/C408): Western Cape—Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town; Tygerberg Hospital, Cape Town; KwaZulu-Natal—Greys Hospital, Pietermaritzburg; Free State—Pelonomi and Universitas Academic hospitals, Mangaung Metro (Bloemfontein); Gauteng—Chris Hani Baragwanath Academic Hospital, Wits Donald Gordon Medical Centre, and Nelson Mandela Children's Hospital (NMCH), Johannesburg. All participating PICUs admit patients living predominantly in low socio-economic circumstances. Private, for-profit hospitals were not included as study sites. Neonates within the first month of life and preterm infants less than 36 weeks postconceptional age were excluded. Any repeat admissions were included as separate cases. Anonymized data were collected on the 15th day of each month (±1 d), for 6 months from February to July 2022, using a standardized, centralized Research Electronic Data Capture (REDCap) database (v11.0.3, May 14, 2021; Vanderbilt University, Nashville, TN). The same study subinvestigators collected data over the entire study period.

The following data were collected prospectively as mandatory fields from participants' clinical charts and hospital files on allocated study days: dates of birth, PICU admission, and study day; sex; documented admission weight and calculated weight for age Z score; emergency or elective admission; primary diagnostic category (respiratory, cardiac, gastrointestinal, neurological, trauma, sepsis, and general surgery); date of admission to the PICU; presence of comorbid conditions (chronic lung disease, ex-preterm, HIV infection or exposure, genetic/congenital disorders, cardiac disorders, other); admission Pediatric Index of Mortality 3 (PIM3) fields; current vital signs over a period of stability (heart rate, blood pressure, respiratory rate, oxygen saturation); whether the patient was receiving neuromuscular blockade on the study day; the most recent blood gas measurements on the study day; and current ventilation and oxygenation settings. Chest x-rays were taken routinely at all sites and evaluated by attending physicians, who were required to tick (Y/N) if the patient complied with the 2015 PALICC age, timing, origin of edema, and chest imaging requirement for pARDS (11). The diagnosis of pARDS was then made by a REDCap algorithm, using the collected data to evaluate all components of the 2015 PALICC criteria (11). Patients with pARDS were further categorized as mild, moderate, or severe (5). Where arterial blood gases (ABG) within the previous 12 hours were not available for the calculation of Pao_2/Fio_2 and oxygenation index, oxygen saturation was used to calculate Spo_2/Fio_2 and oxygenation saturation index, with study sites instructed to titrate Fio_2 to maintain Spo_2 less than or equal to 97% as standard practice (5). Site investigators received a standardized "users guide" to inform data collection fields and PALICC criteria.

Assuming a 5% prevalence of pARDS, with 95% CI and 5% precision, an estimated sample size of 73 patients was calculated as being required to determine prevalence (12). Recruitment was planned to continue for at least 6 months, including both summer and winter months, or until 50 children with pARDS were identified, to describe and compare the characteristics of children with and without pARDS.

Prevalence was calculated as *n* (number of patients with pARDS at all study sites)/*N* (total number of children admitted to all study sites at the same time points). After testing for normality using the Shapiro-Wilks W test, descriptive statistics were used to summarize the data using measures of central tendency and counts (percentage) for continuous and categorical variables, respectively. Tests of association between patients with and without pARDS were evaluated using Mann-Whitney *U* tests for continuous and Chi-square (χ^2) tests for categorical variables. Variables identified as being associated with having pARDS, at a significance level of *p* value of less than 0.1, were entered into a best-fit multivariable binary logistic regression model to identify independent associative factors. Variables included in the classification of pARDS were excluded from the multivariable analysis. Exploratory analyses of associations with pARDS severity were conducted using χ^2 tests for categorical, and Kruskal-Wallis tests for continuous variables. A post hoc sensitivity analysis was performed to examine the effect of cardiac disease on pARDS prevalence, excluding all patients with primary or comorbid cardiac disease. The statistical significance was set at *p* value of less than 0.05, with Bonferroni correction applied for multiple comparisons on univariate analysis. IBM SPSS Statistics (version 28.0.1.0; 2021; IBM Corporation, New York, NY) was used for all data analyses.

RESULTS

A total of 310 patients (166, 53.5% male; median (IQR) age 9.8 [3.1–32.9] mo) were present in the study PICU on data collection days. The majority (219; 70.6%) of patients were under two years and 174 (56.1%) were under one year of age. Patients had mostly been admitted as emergencies (243; 78.4%), with respiratory (124; 39.9%) and cardiac (53; 17.0%) disease, and the presence of one or more comorbid condition was common (184 [59.4%] (**eTables 1** and **2**, http://links.lww.com/PCC/C408).

Patients had been admitted to the PICU for median (IQR) 6 (2–12) days at the time of data collection (eTable 1, http://links.lww.com/PCC/C408). One hundred ninety-five patients (62.9%) were invasively mechanically ventilated on study days, using the following modes: high-frequency oscillation (22; 11.3%), pressure control (147; 75.4%), pressure-regulated volume control (2; 1.0%), pressure support (15; 7.7%), volume control (2; 1.0%), biphasic positive airway pressure (2; 1.0%), and not reported or other (5; 2.6%). An additional 13 (4.2%) were on noninvasive ventilation.

A total of 176 (56.8%) patients had ABG analyses, whilst for the remaining 134 patients (43.2%)

transcutaneous oxygen saturation was used for the pARDS identification. Seventy-one (22.9%) patients were classified as being "at risk" of pARDS according to 2015 PALICC criteria (5), whereas 95 patients, with a calculated prevalence of 30.6% (95% CI, 24.7–37.5%), fulfilled pARDS criteria. Severity of pARDS was classified for those on invasive mechanical ventilation (n = 92): mild (53, 58.2%), moderate (23, 25.3%), and severe (16, 17.6%) (**Fig. 1**). Of the 208 patients receiving invasive or noninvasive mechanical ventilation on study days, 95 (45.6%) met pARDS criteria (eTable 1, http://links.lww.com/PCC/C408).

On univariate analysis, children with pARDS had higher PIM3 risk of mortality than those without pARDS (including those "at risk" of pARDS), with no significant difference in age, weight, sex, emergency vs elective admission, or presence of a comorbidity (eTable 1, http://links.lww.com/PCC/C408). A greater proportion of patients with pARDS were admitted for respiratory disease, specifically pneumonia (eTable 2, http://links.lww.com/PCC/C408), whilst the difference in the proportion of other diagnostic categories did not reach Bonferroni adjusted significance levels between pARDS and non-pARDS groups (eTable 1, http://links.lww.com/PCC/C408). There was no significant difference in pARDS prevalence amongst study days throughout the study period (χ^2 = 5.5; p = 0.36). The proportions of patients with and without pARDS varied across study sites, with prevalence ranging between 14.3% (n/N 7/49) at NMCH and 93.8% (n/N 15/16) at Greys Hospital (χ^2 = 39.2; p < 0.001; **Fig. 2**). The prevalence of pARDS at RCWMCH, which contributed the greatest number of participants, was 29.6% (n/N 32/108).

A multivariable logistic regression was performed to ascertain the effects of the study site, primary admission diagnostic category, presence of comorbidity/comorbidities, and PIM3 risk of mortality score on the likelihood that patients had pARDS. The logistic regression model was statistically significant (χ^2 = 43.72; p < 0.001) and a good fit for the data (Homer and Lemeshow χ^2 = 5.54; p = 0.70). The model explained 21.6% (Nagelkerke R^2) of the variance in pARDS and correctly identified 75.5% of cases. Patients admitted for management of a respiratory condition were 2.6 times more likely to have pARDS than those with other conditions (adjusted odds ratio [aOR] 2.64; 95% CI, 1.27–5.48; p = 0.01). Increasing risk of mortality on admission to PICU was associated with an increased likelihood of pARDS (aOR 1.02; 95% CI, 1.00–1.04; p = 0.04). There were no significant associations between any other variable in the model and the likelihood of having pARDS.

Severity classification of pARDS (mild, moderate, and severe) was significantly associated with admission risk of mortality; receipt of neuromuscular blockade on study days, and male sex (**Table 1**). There was no association with patient age (p = 0.83), admission diagnosis (χ^2 = 15.78; p = 0.78), presence of comorbidity/ies (χ^2 = 1.64; p = 0.65), emergency versus elective admission (χ^2 = 1.24; p = 0.74), study site (χ^2 = 18.86; p = 0.59), or ventilator day (p = 0.39).

The post hoc sensitivity analysis, excluding all patients with primary or comorbid cardiac disease yielded an adjusted prevalence of 80/235 (34.04%; 95% CI, 28.01–40.49%).

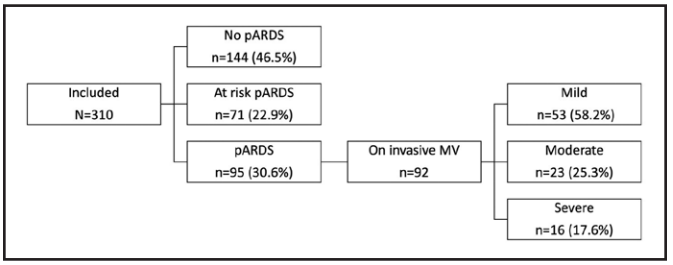

Figure 1. Flow of participants through the study. MV = mechanical ventilation, pARDS = pediatric acute respiratory distress syndrome.

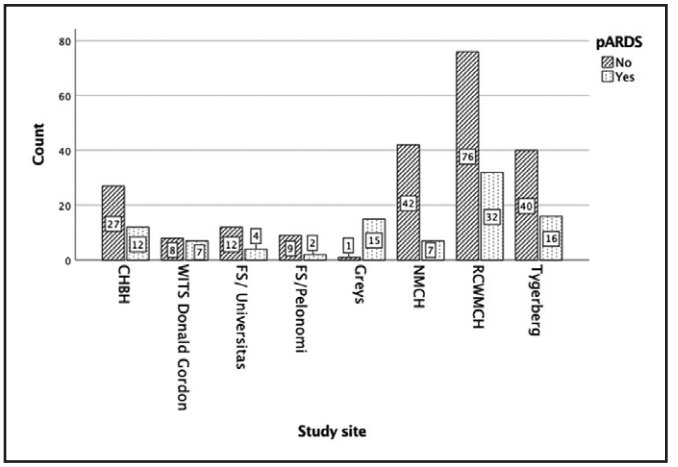

Figure 2. Pediatric acute respiratory distress syndrome (pARDS) prevalence per study site (χ^2 = 39.2; p < 0.001). CHBH = Chris Hani Baragwanath Hospital, FS = free state, NMCH = Nelson Mandela Children's Hospital, RCWMCH = Red Cross War Memorial Children's Hospital.

TABLE 1.
Variables Associated With Pediatric Acute Respiratory Distress Syndrome Severity (*n* = 92)

Variable	Pediatric Acute Respiratory Distress Syndrome Severity			*p*
	Mild, *n* = 53	Moderate, *n* = 23	Severe, *n* = 16	
Male sex	25 (47.2%)	19 (82.6%)	10 (62.5%)	0.036
Admission risk of mortality (%)	5.14 (3.20–7.84)	5.63 (3.50–16.12)	12.06 (2.72–33.56)	0.009
Receipt of neuromuscular blockade on study day	1 (1.9%)	6 (26.1%)	8 (50.0%)	< 0.001

DISCUSSION

This study reports a 30.6% prevalence of pARDS across multiple PICUs in South Africa, substantially higher than previous reports from other socio-geographic settings, and ten-fold higher than the incidence reported in the PARDIE study (5). Being admitted for the management of respiratory disease and increased risk of mortality (using PIM3) on admission were independently associated with an increased likelihood of having pARDS. A greater proportion of males and patients who received neuromuscular blockade on study days had moderate or severe pARDS compared to mild pARDS. Increasing admission predicted risk of mortality was associated with increased pARDS severity.

Whilst previous studies have reported pARDS occurring in between 3% (prospective multisite incidence study) and 9.9% (retrospective single-site prevalence study) of PICU admissions in different settings (5, 13, 14); Lozano et al (2023) reported a 30.3% pARDS prevalence in a study conducted during the COVID-19 pandemic at RCWMCH in South Africa, one of the PICUs contributing the highest patient numbers to this multicenter study (8). This study validates the previous single-center report, with similar results within RCWMCH alone (29.6%) as well as overall prevalence across the study sites (30.6%). The high burden of pARDS in South African PICUs highlights the need for further epidemiological and therapeutic research within Africa and other resource-constrained settings, as recommended by the PALICC2 initiative (6, 7). This multicenter study highlights the different patient profiles in South African PICUs. Similar to the previous single-site study (8), most patients were under 2 years of age, and the median age was under 1 year, compared with a median of 3.3 years of age in the PARDIE study sites (5). There was also a higher PIM3 probability of mortality in this study (4.4% compared with 3.2% in PARDIE [5]), possibly associated with the high rate of emergency and nonsurgical admissions as well as social determinants of health and delays in accessing tertiary healthcare services in South Africa, which have been reported previously (15). Of concern, almost a quarter of children in this cohort were severely underweight for age, although this factor was not found to be significantly associated with pARDS. Children in sub-Saharan Africa have the highest under-five mortality rates in the world, with an estimated 74 deaths per 1,000 live births, compared with 37 per 1,000 live births globally (16). This is approximately 14 times higher than the mortality risk for children living in Europe and North America (16), the major contributors to PARDIE (5). Despite this, Southern Africa has extremely scarce and unequally distributed pediatric

AT THE BEDSIDE

- The prevalence of pediatric acute respiratory distress syndrome in South African PICUs is up to 10-fold higher than previous international reports.
- Clinicians should be aware that respiratory disease, which is a major cause of under-five mortality in South Africa, is also the most common trigger condition for the development of pARDS.
- This study paves the way for prospective epidemiological studies in critically ill South African children to describe the natural history and outcomes of pARDS, inform clinical trials, and optimize management strategies.

and adult intensive care resources serving a large population (17, 18). The need for PICU beds in one South African province (KwaZulu-Natal) was estimated to be 23.7 per 100,000 children, with actual PICU bed availability of only 0.73 of 100,000 children (19). The notably higher pARDS prevalence documented in the small Greys Hospital site (Fig. 2) in KwaZulu-Natal reflects the scarcity of PICU resources in this region. The competition for PICU beds and intensive care interventions such as invasive ventilation in South Africa results in many children receiving noninvasive ventilatory support in pediatric wards outside the PICU. This may have led to an unintended selection bias toward sicker children in this study, evidenced in the high admission risk of mortality in this cohort as well as the 46% pARDS rate in mechanically ventilated children, compared to the 6% incidence reported in PARDIE (5). Future pARDS research should therefore include children managed outside the PICU.

The proportions of children admitted with any comorbidity were similar between PARDIE and our study (5); however, the proportions of pARDS trigger conditions differed, with surprisingly lower proportions of sepsis and respiratory infection in our cohort. Importantly, we included all children with cardiac disease, considering PALICC recommendations (11), whereas PARDIE excluded patients with cyanotic heart disease and those recovering from cardiac surgery (5). Considering our sensitivity analysis excluding patients with cardiac disease showed a higher prevalence of 34%, this is unlikely to explain the disparity between studies. Another important methodological difference between the studies is that PARDIE excluded patients who had met pARDS diagnostic criteria during the current admission before screening, to identify new cases (incidence) (5), whereas we included all patients meeting criteria on the study day to determine pARDS prevalence.

It is important to identify the subphenotypes (observable clinical and physiological characteristics) (20) of patients who are at increased risk of pARDS to plan for regional preventive or interventive strategies (21). Although we did not evaluate specific biomarkers and were unable to identify patients falling into the hyperinflammatory or hypoinflammatory phenotypes, which should be considered in future research, we did identify significant associations between pARDS and both respiratory disease and admission risk of mortality (using PIM3). We did not collect data that could be used to indicate multiple organ dysfunction at the time of inclusion in the study, which is recommended for future pARDS research. Pneumonia is the primary cause of pARDS globally (5, 22) and in South Africa, it is one of the leading causes of under-five mortality (23, 24). Considering that pneumonia was also the most common pARDS trigger condition in our cohort, this study highlights the importance of prevention, early recognition, and appropriate management of children with severe respiratory disease. The lack of significant seasonal fluctuation of pARDS prevalence, which was expected given the increased burden of viral respiratory disease over the winter months (25), may be a consequence of not sampling over complete seasons. A previous South African study also reported that some of the commonest respiratory viruses did not show clear seasonal trends (26). Future studies should aim to continue for a full year to determine pARDS seasonality. Considering we did not prospectively follow children from admission, we cannot comment on the course of pARDS. Furthermore, it cannot be determined whether the high admission risk of mortality was related to patients already having or being at risk of pARDS at admission, or whether children with high illness severity are more likely to develop pARDS during the course of their critical illness. This requires further prospective investigation.

A number of studies have reported an association between both pARDS trigger conditions and comorbidities (20), particularly pre-existing immunodeficiencies, on pARDS severity and outcomes (11). In contrast, we found no significant associations between either admission diagnostic category or comorbidities (including HIV infection and exposure) and pARDS severity. Although there was no overall significant association between the male sex and pARDS, which has been previously reported (11, 27–31), there was an association between male sex and pARDS severity, supporting the previous suggestion of increased respiratory morbidity in males compared with females (32).

This study was adequately powered to evaluate prevalence and was strengthened by the multicenter study design, thereby improving external validity at a country level. The generalizability to other middle-income countries with high levels of inequality and poverty is; however, not clear. Study sites were selected

on a convenience basis, which introduces the potential for selection bias and is thus a limitation of the study. The majority of data were contributed by PICUs in the two main provinces (Gauteng and Western Cape), in alignment with the disparity of PICU bed availability in the country; whereas the province with the third highest proportion of intensive care beds (KwaZulu-Natal) was under-represented in this study (18), with the 14-bedded PICU Inkosi Albert Luthuli Central Hospital (19) not volunteering to participate. The included study sites represent the majority (> 60%) of the currently available not-for-profit, dedicated PICU beds in the country. We were unable to standardize the time of day that data collection occurred across all study sites, which might have affected study findings. For example, the proportion of emergency versus elective patients may vary at different times of the day. All study sites are tertiary level PICUs and except for NMCH, which is a nongovernmental organization, are publicly funded and mainly serve lower socio-economic sectors of the population. Exclusively private facilities catering to the middle and upper-income sector were not included, and the results of this study may not be generalizable to the PICUs serving the relatively well-resourced population groups within South Africa. We did not standardly collect specimens or document laboratory culture results and cannot comment on etiological agents. Furthermore, granular chest imaging findings were not documented, and these are further limitations of the study. We did not collect longitudinal data to document the progression of pARDS over time, and thus the true incidence, natural history, and outcomes of the condition could not be evaluated. These are important areas for future study in South Africa. Just over half the participants had ABG analyses available at the time of pARDS diagnosis, similar to PARDIE (5). The use of pulse oximetry to diagnose pARDS is recommended where ABG is not available (6, 7); however, this requires validation in the pediatric African setting (33).

In conclusion, this multicenter observational study reports an extremely high prevalence of pARDS in South African PICUs, up to 10-fold higher than previous global reports. Further prospective epidemiological research is needed to determine the natural history and outcomes of pARDS in South African children admitted to hospital, as well as identify appropriate targeted pulmonary and nonpulmonary interventions for the prevention and management of pARDS in this high-risk population group.

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Dr. Morrow was involved in study conceptualization; data curation and analysis; study design and methodology; study administration; and preparation of all article drafts. Ms. Lozano Ray and Drs. Culloch, Salie, and Argent were involved in the study conceptualization and critical review of article drafts. Drs. Salloo, Appel, Du Plooy, Cawood, Moshesh, Keeling, Solomon, Hlophe, Demopoulos, Parker, Khan, and Naidoo were involved in the study conceptualization, data collection, and critical review of article drafts.

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