

*Background* The off-label use of drugs to treat children is a global practice attributed to the traditional exclusion of children from clinical trials mainly due to practical and ethical reasons. Off-label drug use carries both benefits and risks, but data regarding this use pattern are scanty in sub-Saharan Africa. *Objective* To determine the incidence and predictors of off-label antibiotic use in children less than 5 years admitted at Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda. *Setting* A prospective drug utilisation study was conducted among in-patients at the Paediatric Ward of MRRH from May to June 2019. *Methods* Clinical records and treatment notes of all children aged 0 to 59 months with at least one antibiotic prescription during the admission period were reviewed and included for data collection. Key informant interviews were conducted with physicians attending to patients in the Paediatric Ward. *Main outcome measure* Off-label use and potential predictors of off-label antibiotic use. *Results* Of 427 children admitted to the Paediatric Ward, 165 (38.6%) received 366 antibiotic prescriptions. However, 359 prescriptions belonging to 162 patients were analyzed. Off-label prescriptions occurred in 18.9% (95% CI: 14.9–23.0) of antibiotic prescriptions. Two categories of off-label prescriptions were found: off-label frequency of administration (n = 55, 80.9%), and off-label doses (n = 13, 19.1%). Ceftriaxone was the most common antibiotic prescribed at off-label doses, (n = 6, 8.8%) while ampicillin was the most common antibiotic prescribed with an off-label frequency of administration, (n = 39, 57.3%). Infants (1–23 months) received the majority (47.1%) of off-label antibiotic prescriptions; neonates (0–28 days) received 27.9%, and children (24–59 months) received 25% of the prescriptions. Controlling for sex and disease severity, age category remained significantly associated with off-label antibiotic use on multivariate analysis. *Conclusion* Off-label frequency of administration was the major category of off-label drug use, while off-label dose was the minor category. Age was a significant factor for off-label antibiotic prescription, with infants receiving the highest number of off-label prescriptions. Attending physicians identified several justifiable circumstances that warrant off-label antibiotic use and support emerging “well-founded” off-label uses of antibiotics in different paediatric age groups