

Clinical Prediction Rule to Guide Diagnostic Testing for *Shigellosis* and Improve Antibiotic Stewardship for Pediatric Diarrhea

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Background. Diarrheal diseases are a leading cause of death for children aged <5 years. Identification of etiology helps guide pathogen-specific therapy, but availability of diagnostic testing is often limited in low-resource settings. Our goal is to develop a clinical prediction rule (CPR) to guide clinicians in identifying when to use a point-of-care (POC) diagnostic for *Shigella* in children presenting with acute diarrhea.

Methods. We used clinical and demographic data from the Global Enteric Multicenter Study (GEMS) study to build predictive models for diarrhea of *Shigella* etiology in children aged ≤59 months presenting with moderate to severe diarrhea in Africa and Asia. We screened variables using random forests, and assessed predictive performance with random forest regression and logistic regression using cross-validation. We used the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study to externally validate our GEMS-derived CPR.

Results. Of the 5011 cases analyzed, 1332 (27%) had diarrhea of *Shigella* etiology. Our CPR had high predictive ability (area under the receiver operating characteristic curve = 0.80 [95% confidence interval, .79–.81]) using the top 2 predictive variables, age and caregiver-reported bloody diarrhea. We show that by using our CPR to triage who receives diagnostic testing, 3 times more *Shigella* diarrhea cases would have been identified compared to current symptom-based guidelines, with only 27% of cases receiving a POC diagnostic test.

Conclusions. We demonstrate how a CPR can be used to guide use of a POC diagnostic test for diarrhea management. Using our CPR, available diagnostic capacity can be optimized to improve appropriate antibiotic use.

Keywords. clinical prediction rule; diagnostic testing; diarrhea; point-of-care test; *Shigella*.

Despite medical advancements, diarrheal diseases remain a leading cause of death in children aged <5 years, with an estimated 960 million cases and 500 000 deaths worldwide, most of which occur in low- and middle-income countries (LMICs). While most episodes of diarrhea are self-limiting and treatment with oral rehydration adequate, antibiotics can reduce the severity and duration of some diarrhea etiologies, including

Shigella spp, the cause of shigellosis [1, 2]. Therefore, the World Health Organization's (WHO) 2014 updated Integrated Management of Childhood Illness (IMCI) recommends antibiotics for treatment of presumptive *Shigella* spp infection with severe diarrhea [3, 4]. In practice, antibiotics may also be administered for presumptive shigellosis if the patient is malnourished, even in the absence of IMCI-indicated diarrhea-associated symptoms. Conversely, antibiotics can be expensive and may cause adverse effects, including hypersensitivity reactions, nausea, and prolonged symptoms for other diarrhea etiologies [5], and overuse of antibiotics can contribute to antimicrobial resistance [6–12]. Given changing resistance patterns, diarrhea etiology can inform antibiotic choice. Therefore, accurately identifying the etiology or cause of diarrhea is vital for proper management at the individual level and appropriate public health responses at the population level.

Laboratory-based diagnostics such as stool culture and polymerase chain reaction (PCR) remain the most commonly used methods of identifying diarrhea etiology, including *Shigella* spp [13–15]. Unfortunately, currently available laboratory

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