

1 **Prolonged and persistent diarrhoea is not restricted to children with acute malnutrition: an**
2 **observational study in Ethiopia**

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24

25 **Abstract**

26 **Objectives**

27 Persistent (PD, defined as diarrhoea lasting ≥ 14 days) and prolonged diarrhoea (ProD, defined as diarrhoea
28 lasting 7-13 days) are assumed to be closely linked to acute malnutrition. Improved treatment relies on better
29 characterization of these diarrhoeal syndromes. Our objective was to assess the prevalence of prolonged and
30 persistent diarrhoea, to estimate their co-occurrence with acute malnutrition and association with demographic
31 and clinical factors.

32
33 **Methods**

34 We conducted a case-control study where cases were children under 5 years of age with diarrhoea and controls
35 were children without diarrhoea, frequency matched weekly by age and district of residency. Controls for cases
36 0-11 months were recruited from vaccination rooms and controls for cases 12-59 months were recruited by
37 house visits using random locations in the catchment area of the study sites. Data were analysed by mixed
38 model logistic regression.

39
40 **Results**

41 We enrolled 1134 cases and 946 controls. Among the cases, 967 (85%) had acute diarrhoea (AD), 129 (11%)
42 had ProD and 36 (3.2%) had PD. Cases more often had acute malnutrition at enrolment (17% vs 4%, $p < 0.0001$)
43 and were born prematurely (5.7% vs 1.8%, $p < 0.0001$) compared with controls. Seventy-five percent of ProPD
44 cases did not have acute malnutrition. Cases with AD and ProPD had different symptomatology, even beyond
45 illness duration.

46
47 **Conclusions**

48 ProPD is common among children presenting with diarrhoea and is not confined to children with acute
49 malnutrition. There is an urgent need for studies assessing causes of ProPD with and without acute malnutrition
50 to develop treatment guidelines for these conditions.

51 **Introduction**

52 Most guidelines and studies on childhood diarrhoea in low- and middle-income countries focus on causes and
53 management of acute diarrhoea (AD), defined as diarrhoea lasting <7 days (1). There is limited knowledge of
54 causes that lead to progression to persistent diarrhoea (PD), defined as diarrhoea lasting ≥ 14 days, despite its
55 major contribution to diarrhoeal deaths (2). Prolonged diarrhoea (ProD), defined as diarrhoea lasting 7-13 days,
56 has attracted interest as it substantially increases the risk of PD (3). ProD accounts for around 10% and PD for
57 approximately 5% of all diarrhoea cases but estimates vary greatly (3-5).

58 Researchers agree that there is a close link between malnutrition and extended duration of diarrhoea (3, 6) and
59 while limited data is available, it has previously been suggested that prevention and treatment of malnutrition
60 might reduce the incidence of PD (7). Diarrhoea of longer duration is common in children with severe acute
61 malnutrition (SAM) (8), but the prevalence among children with moderate acute malnutrition (MAM) is
62 unknown. Moreover, there are few reports on the proportion of MAM and SAM among patients with prolonged
63 or persistent diarrhoea (ProPD), i.e. diarrhoea lasting at least 7 days.

64 While there are clinical management guidelines available for children with SAM, there are not yet any
65 international treatment recommendations for MAM and only a technical note with suggestions (9, 10). It is not
66 clear how best to manage children who also have ProPD, or how best to treat ProPD in children who do not
67 have MAM or SAM. The recommended treatment for PD includes a specific nutritional regimen, which is
68 quite complex and has not been implemented widely (11, 12). Although some studies reported a positive effect
69 of nutritional interventions (13-15), there are no specific recommendations for the treatment of ProD (1, 12,
70 16).

71 Under the assumption that nutritional status is one of the key host prognostic factors in diarrhoea, a better
72 understanding of the distinction between ProPD, MAM and SAM is needed for evidence-based treatment
73 algorithms tailored to each of these partially overlapping and vulnerable groups. Previous studies have
74 identified risk factors for PD (17-19) and ProD (3, 20), however most of these studies were conducted over
75 two decades ago before the current definition of acute malnutrition and did not include MAM or distinguish
76 between MAM and SAM.

77 The objective of this study was to estimate the proportion of ProPD among children with diarrhoea and to
78 estimate how many of them had acute malnutrition. We compared cases with diarrhoea with non-diarrhoea
79 controls and we furthermore aimed to describe factors associated with ProPD with a primary focus on acute
80 malnutrition, by comparing children with ProPD with children with AD.

81 **Methods**

82 **Study design and participants**

83 The study was a case-control study in South Eastern Ethiopia. Cases were children under 5 years of age with
84 diarrhoea of any duration, seen at Jimma University Specialized Teaching Hospital (JUSTH) or Serbo Health
85 Centre (SHC). Children residing outside the 15 districts defining Jimma Town and its catchment area or the 8
86 districts defining the SHC catchment area were excluded. JUSTH is a tertiary referral hospital and SHC covers
87 a neighbouring area approximately 16 km away. Children with diarrhoea were enrolled whether or not
88 diarrhoea was the primary complaint leading them to seek health care. Exclusion criteria were enrolment as a
89 case within the last 60 days and admission as an inpatient for longer than 24 hours prior to enrolment. Cases
90 were enrolled from February 2017 till July 2018, from morning till evening seven days a week at JUSTH and
91 during working hours on weekdays at SHC.

92 Controls without diarrhoea in the previous 48 hours were found by frequency matching by geography of
93 household, age group and time. Age groups were 0-5 months, 6-11 months, 12-23 months, and 24-59 months.
94 In JUSTH controls were recruited from any of the 15 districts defined as JUSTH catchment area and in SHC
95 from a random sample of the districts that cases had been enrolled from during the preceding week. Controls
96 in the age groups 0-5 and 6-11 months were recruited from vaccination rooms at the two sites. A control was
97 eligible if the child came from one of the 15 districts in JUSTH catchment area, or from one of randomly
98 selected districts in the SHC catchment area based on that week's control plan. If it was not possible to enrol
99 the control in the 0-5 or 6-11-month age categories from the vaccination room within one week after frequency
100 matching, they were recruited from the community instead, in the following week. The controls for the 12-59
101 months old patients were recruited in the community. We identified eligible community controls by randomly
102 selecting a GPS point in the JUSTH catchment area or in the randomly selected district in the SHC catchment
103 area, by using QGIS v2.18 (21) and district borders from ArcGIS (22). The GPS point was plotted on Google
104 Earth (23) and selected if there was a road within 300 meters of the point accessible by a motorbike (defined
105 as any visible path minimum 2 m wide). The study nurse travelled to the GPS location, or as close as possible
106 based on the road conditions, then stopped, and faced in a pre-specified random compass direction. The house
107 nearest to this direct line, in walking distance, was selected. If no child of the required age lived in the first
108 house, or if the caregiver refused, the steps above were repeated, but this time with that house as the starting
109 point. If an eligible child resided in the house, but could not be found in two attempts, the procedure was
110 repeated. If the listed control had not been enrolled within two weeks after frequency matching, that control
111 was dropped, except in a few circumstances where controls had to be enrolled in the third week, because of
112 unexpected disruptions of study activities.

113 Initially, the case-control ratio was 10:6 (6 controls for 10 cases), but from July 2017 it was changed to 1:1
114 due to more cases coming from outside the catchment areas and due to a lower caseload than expected. To

115 determine factors associated with diarrhoea we compared cases and controls; to determine factors associated
116 with longer duration of diarrhoea, we compared cases with ProPD with cases with AD.

117 **Data collection**

118 Demographic and clinical data were collected using standardized case report forms. Before returning home,
119 information on treatment and clinical status was collected by the study nurse or from the hospital medical
120 records. If diarrhoea had lasted for less than 14 days at the time of enrolment, the study nurses contacted the
121 caregivers by phone 14 days after the onset of diarrhoea to assess progression to ProD or PD. Follow-up visit
122 to the paediatric outpatient's department was encouraged for all additional ProD and PD cases identified this
123 way. All cases were offered HIV testing; first-line testing was conducted with the First Response™ HIV 1-2-
124 O Card test (Premier Medical Corporation Ltd, Daman, India); for children younger than 18 months, positive
125 test results were confirmed by PCR and for children older than 18 months, positive results were confirmed by
126 a second HIV test kit, Uni-Gold™ HIV (Trinity Biotech Manufacturing Ltd, Co. Wicklow, Ireland). HIV
127 counselling and testing was done by routine clinical staff or study nurses trained in HIV counselling and
128 testing. Information to caregivers and HIV treatment to children were offered according to routine care.

129 **Definitions**

130 Diarrhoea was defined as the passage of three or more watery or loose stools within the preceding 24 hours;
131 the presence and duration of diarrhoea was assessed by caregiver recall. Diarrhoea that had lasted 14 days or
132 longer was defined as PD, diarrhoea of 7-13 days' duration as ProD and diarrhoea lasting <7 days as AD.
133 Dysentery was defined as at least one loose stool per day with visible blood in the previous 24 hours. SAM
134 was defined as one or more of the following: weight-for-height z-score (WHZ) ≤ -3 of the WHO standard
135 curves (24), and/or mid-upper arm circumference (MUAC) ≤ 115 mm and/or presence of bilateral oedema
136 involving at least the feet. MAM was defined as a WHZ ≤ -2 and > -3 or a MUAC ≤ 125 mm and > 115 mm
137 with no oedema. For children below 6 months, only WHZ ≤ -2 and presence of bilateral oedema was used to
138 define SAM and MAM. HIV status was either based on HIV testing on enrolment or by previous testing as
139 reported by the caregiver. Children below 18 months with an HIV positive mother was considered HIV
140 exposed and uninfected if a PCR result for the child was negative or not available. Stunting was defined as a
141 length/height-for-age z-score ≤ -2 of the WHO standard curves (24). A child had moderate to severe diarrhoea
142 if they had diarrhoea together with very sunken eyes, an abdominal skin pinch as assessed by the research
143 nurse to go back slowly (abnormal but ≤ 2 s) or very slowly (> 2 s), had dysentery, received IV fluids or was
144 admitted for any reason (25). Fever was defined as an axillary temperature $\geq 37.5^\circ\text{C}$. Access to "improved
145 water" was defined as having the main source of drinking water for the household as either a private tap in the
146 house, public tap, rainwater collected in a container, or borehole/protected spring. A Water/sanitation, Assets
147 and Maternal education (WAM) index was calculated similarly as in the MAL-ED study; access to "improved"
148 or "unimproved" water and/or sanitation, the presence or absence of eight household assets and maternal

149 education (26). Rotavirus vaccine in Ethiopia is an oral vaccine (Rotarix™) that is given twice, usually at 6
150 weeks and 10 or 14 weeks of age. We defined the child as vaccinated against rotavirus if two doses had been
151 received at least four weeks apart.

152 **Statistical methods**

153 Double data entry was done with EpiData 3.1 (EpiData, Odense, Denmark) and data analysis with SAS
154 Enterprise Guide, Version 7.11 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). A p
155 value lower than 0.05 was considered to represent statistical significance and 95% confidence intervals were
156 used to represent statistical precision. We used an unconditional mixed model logistic regression, adjusted for
157 age and with random effects for district of residency and enrolment month, for binary outcomes. In case of
158 problems with convergence the district of residency variable was excluded. We used these models for both the
159 comparison between cases and controls, and for comparisons between different groups of cases. Since two
160 different methods were used to enrol controls, we assessed each variable for interaction with age group (0-11
161 months versus 12-59 months) and presented stratified analyses in case of a significant interaction.

162 Because the infancy controls were recruited from vaccination rooms, we did not include analysis of rotavirus
163 vaccination in the comparison between cases and controls. Furthermore, since length and height were not
164 measured among controls in the community, we excluded the analysis of WHZ and stunting in the comparison
165 between cases and controls.

166 **Ethical issues**

167 Jimma University IRB (Reference: RPGC/610/2016), the Ethiopian National Research Ethics Review
168 Committee (Reference: JU JURPGD/839/2017) and the Regional Committee for Medical and Health Research
169 Ethics of Western Norway (Reference: 2016/1096) approved the study. Children were eligible after obtaining
170 written informed consent from the caregivers (thumbprint signature for caregivers who could not read or write).

171

172 **Results**

173 Of 1413 cases screened, 1156 (82%) were eligible, and of these 1134 (98%) were enrolled in the study (figure
174 1). The main reasons for ineligibility was residency outside catchment area (n=161), refusal (n=48) and
175 enrolment as a case during the last 60 days (n=33). Using weekly case enrollment lists, and after the frequency
176 matching procedure had been completed, we had weekly target lists that in total comprised 979 controls. Of
177 these, 20 controls were not enrolled, since a suitable control had not been successfully enrolled within the
178 enrollment window because of unexpected staff shortages or disruption of study activities. Of the 959
179 remaining controls 946 (99%) were enrolled (figure 1). Of the enrolled controls, 935 (99%) were enrolled
180 within two weeks and the remaining 11 in week three. Of all the enrolled children, 11 controls and 21 cases
181 had previously been enrolled as either a case >60 days earlier or as a control. Three hundred and thirty-eight
182 (30%) the cases were enrolled before the change in case-control ratio from 10:6 to 1:1. Only two cases (0.2%)
183 were HIV exposed.

184 On enrolment, 967 (85%) of the cases had AD, 129 (11%) had ProD and 36 (3.2%) had PD. Eighty-seven
185 cases (8%) had dysentery. Eleven cases (1%) were admitted and five (0.4%) died, of whom one had ProD and
186 four AD.

187 We found that 25% of cases with ProPD had MAM or SAM, and that acute malnutrition was more frequently
188 present among cases with ProPD than with AD (OR 1.85, 95%CI 1.23, 2.79) (figure 2). Yet, of the 164 cases
189 with ProPD (anthropometric data not available for one case), 123 (75%) did not have any form of acute
190 malnutrition (figure 2).

191 **Factors associated with any diarrhoea**

192 In the adjusted analysis we found that MUAC \leq 125 mm (OR 4.58, 95%CI 2.64, 7.97), being born prematurely
193 (OR 2.22, 95%CI 1.27, 4.28), or having visited a health facility in the previous month (OR 1.43, 95%CI 1.14,
194 1.79) was associated with having diarrhoea (table 1). A low WAM index was negatively correlated with
195 diarrhoea (OR 0.80, 95%CI 0.66, 0.98). Taking re-enrolment into account had negligible effect on the
196 estimates. HIV status/exposure was not included in the model due to low prevalence. Interactions with age
197 group (age < 12 vs \geq 12 months), defined as heterogeneity of ORs were found for the following variables;
198 MUAC (3.07 (1.91, 4.95) vs 5.31 (2.36, 11.95)), exclusive breastfeeding <6 months (1.32 (0.96, 1.82) vs 0.84
199 (0.66, 1.08)), born prematurely (1.47 (0.70, 3.08) vs 7.03 (2.73, 16.10)) and WAM index (1.15 (0.88, 1.51) vs
200 0.45 (0.34, 0.58)).

201 **AD compared with ProPD**

202 Among diarrhoea cases we found in the adjusted analysis that MUAC \leq 125 mm (OR 2.10, 95%CI 1.05, 4.22)
203 and stunting (OR 1.99, 95%CI 1.16, 4.22) were associated with ProPD (table 2). Treatment with zinc also
204 correlated with ProPD (OR 3.49, 95% CI 1.71, 7.12). Lastly, we found a trend that fever upon enrolment (OR

205 0.45, 95%CI 0.20, 1.04) and history of vomiting (OR 0.63, 95%CI 0.39, 1.02) correlated with AD. Taking re-
206 enrolment into account made little difference to these estimates.

207 To determine whether the estimates of the characterises comparing AD and ProPD cases were related to
208 differences in nutritional status, we performed an additional analysis where we adjusted for wasting and
209 stunting only. This had limited effect on the estimates in the comparison between AD and ProPD (data not
210 shown). We also compared ProPD cases with acute malnutrition and ProPD cases without acute malnutrition
211 and we did not find any clinically relevant difference in the estimates of the demographic and clinical
212 characteristics listed in table 2 (data not shown).

213 A follow-up interview 14 days after onset of the diarrhoeal episodes was successfully completed (96% of these
214 interviews were conducted by phone) in 329 (34%) of the children that presented with AD and 53 (41%) of
215 the cases that presented with ProD. Due to the low phone follow-up and differences between responders and
216 non-responders, the results are not presented.

217 **Discussion**

218 ProPD comprised 14% of the diarrhoea cases, – this is in line with previous studies (3, 4). Since ProPD
219 contributes disproportionately to the total number of diarrhoeal days in a population (27) and a large proportion
220 of diarrhoeal deaths is assumed to be caused by PD (2), more attention needs to be given to these conditions.

221 We found that 25% of cases with ProPD had acute malnutrition. Interestingly, the proportions with acute
222 malnutrition among ProD and PD cases seemed similar and higher than what was observed among the AD
223 cases. This could indicate that grouping ProD and PD together as ProPD may be clinically relevant. The
224 observed proportion of cases with acute malnutrition is similar to the conclusions from a previous study in
225 Bangladesh (28) but comparison with results from older publications is challenging since many of these studies
226 either used definitions of malnutrition that are now outdated or they did not include acute malnutrition, - in
227 particular MAM (17). While we found that a higher proportion of cases with ProPD were acutely malnourished
228 compared with AD, a key observation in our study is that three quarters of the children with ProPD did *not*
229 have acute malnutrition. Other factors may be equally, or more, important for ProPD, including perturbation
230 of the normal gut microbiota (11), environmental enteric dysfunction (27), micronutrient deficiencies (29), or
231 differences in the relative aetiological contribution of various enteropathogens (27).

232 There is a clear need for more clinical and epidemiological studies on ProPD and a major unanswered question
233 is how to best treat children with ProPD in the absence of acute malnutrition (table 3); our results suggest that
234 the majority of ProPD patients fall into this category and are therefore currently left without specific treatment
235 guidelines or with complex recommendations. The guideline for PD cases without malnutrition recommends
236 a complex nutritional treatment regimen that few countries have implemented (12, 30). Furthermore, ProD

237 cases are currently treated as AD cases as no specific recommendations exist and the evidence base is
238 particularly weak in the absence of malnutrition. Whether the current nutritional therapy recommended for
239 MAM and SAM is clinically effective in patients with ProPD should be evaluated in well-designed trials (31).
240 Such trials could form the basis of an update of current guidelines for treatment of diarrhoea in children with
241 acute malnutrition.

242 We found that both acute malnutrition and stunting was more common in children with ProPD than with AD.
243 This does not, however, imply a causal relationship of malnutrition being caused by diarrhoea and could even
244 be explained by ProPD being caused by malnutrition. Our finding of higher average WAM index in cases than
245 in non-diarrhoea controls could be explained by cases representing the segment of the population that can
246 afford to seek health care.

247 Children with AD tended to have a history of vomiting. This has to our knowledge not been described
248 previously. A recent multi-country study found that infections with rotavirus, *Shigella*, *adenovirus* and
249 *Cryptosporidium* were positively associated with fever, vomiting and high stool frequency whereas infections
250 with *Campylobacter* spp. were negatively associated with these signs and symptoms (32). The difference in
251 signs and symptoms between AD and ProPD in our study supports the possibility that the spectrum of
252 enteropathogens that cause AD and ProPD might be different. While it is well-known that the spectrum is
253 overlapping yet different between AD and PD (27), less is known about ProPD combined. Recent studies that
254 used multitarget quantitative PCR assays were able to attribute almost 90% of AD episodes, at a population
255 level, to specific pathogens (33). This contrasts with the sparse knowledge on the aetiology of ProD and PD
256 (27). Further studies could use similar methods to estimate the proportion of ProPD that can be attributed to
257 specific enteropathogens. Substantial differences in aetiological spectrum could be used to develop
258 interventions against specific pathogens including point-of-care diagnostic testing. Fever on enrolment was
259 correlated with AD and likely explained by these cases being in an earlier stage of their disease, when fever is
260 more common.

261 Treatment with zinc was associated with ProPD, a possible explanation is that longer duration of illness
262 increased the likelihood of having received treatment in a health facility before enrolment (34) and that children
263 with AD were treated with zinc in the community and therefore not presenting at our facilities.

264 Besides the association between malnutrition and diarrhoeal duration, previous studies found that use of
265 antibiotics for diarrhoea (18), lack of breastfeeding (17), and young age (19) was associated with PD. The
266 latter two were associated with ProD in a few studies (3, 20). The relative importance of these putative risk
267 factors for ProPD should be established in new studies, as there has been a shift in childhood malnutrition,
268 antibiotic use, treatment of acute malnutrition, and access to health care in recent years (35). We attempted to
269 conduct a phone follow-up among cases to determine how many progressed to ProPD, however with limited

270 success. A recent study in Kenya reported a higher follow-up success rate and reported ProD and PD rates of
271 35% and 7% of the diarrhoea cases, respectively (5). We suggest that future diarrhoea studies should include
272 follow-up; (36); cell phone follow-up warrants further exploration in particular, as it could be developed into
273 a simple and cost-effective tool to reach more children with ProPD.

274 Our study has several limitations. The study was designed to inform clinical care and was therefore conducted
275 in a health-care setting. Data on putative risk factors for diarrhoea was collected retrospectively by interview.
276 Inherent to the retrospective case-control study design is that we cannot reliably make assumptions about the
277 causal direction between factors assessed at enrolment, e.g. malnutrition and diarrhoea. Both health workers
278 and caregivers knew whether the child was a case or a control, which might have affected both the clinical
279 assessments and the caregiver's responses. To limit recall and other information and recall bias, we used a
280 standard case report form for cases and controls that mainly consisted of choosing between predefined answers.
281 Even more importantly, the interviewers were rigorously trained in how to elicit answers independent of
282 whether the child was well or ill.

283 **Conclusion**

284 ProPD is common among children presenting with diarrhoea and is not restricted to children with acute
285 malnutrition. Further studies evaluating the cause of and treatment for ProPD are highly needed.

286

287

288 **Author contributions**

289 MZ, ØJ, NL and KH conceptualized the study. The study was designed by MZ, ØJ, AA, HS, NL and KH. ØJ,
290 AA, MZ and BE led the data collection and all authors contributed to the data analysis and interpretation of
291 data. MZ prepared the first draft of the paper and all authors contributed to the revisions, discussion of results
292 and to the completion of the final manuscript.

293

294 **Declaration of interests**

295 We declare no competing interests.

296

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302

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- 311 1. World Health Organization. Integrated Management of Childhood Illness, Chart Booklet.
312 Geneva,
313 [http://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf?sequence=](http://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf?sequence=16)
314 [16](http://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf?sequence=16): Geneva, World Health Organization,; 2014.
- 315 2. Rahman AE, Moinuddin M, Molla M, Worku A, Hurt L, Kirkwood B, et al. Childhood diarrhoeal
316 deaths in seven low- and middle-income countries. *Bull World Health Organ.* 2014;92(9):664-71.
- 317 3. Moore SR, Lima NL, Soares AM, Oria RB, Pinkerton RC, Barrett LJ, et al. Prolonged episodes of
318 acute diarrhea reduce growth and increase risk of persistent diarrhea in children. *Gastroenterology.*
319 2010;139(4):1156-64.
- 320 4. Lima AA, Guerrant RL. Persistent diarrhea in children: epidemiology, risk factors,
321 pathophysiology, nutritional impact, and management. *Epidemiol Rev.* 1992;14:222-42.
- 322 5. Schilling KA, Omoro R, Derado G, Ayers T, Ochieng JB, Farag TH, et al. Factors Associated with
323 the Duration of Moderate-to-Severe Diarrhea among Children in Rural Western Kenya Enrolled in the Global
324 Enteric Multicenter Study, 2008-2012. *Am J Trop Med Hyg.* 2017;97(1):248-58.
- 325 6. Lima AA, Moore SR, Barboza MS, Jr., Soares AM, Schleupner MA, Newman RD, et al. Persistent
326 diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort
327 study among children in northeastern Brazil. *J Infect Dis.* 2000;181(5):1643-51.
- 328 7. Bhandari N, Bhan MK, Sazawal S, Clemens JD, Bhatnagar S, Khoshoo V. Association of
329 antecedent malnutrition with persistent diarrhoea: a case-control study. *BMJ.* 1989;298(6683):1284-7.
- 330 8. Bhutta ZA, Hendricks KM. Nutritional management of persistent diarrhea in childhood: a
331 perspective from the developing world. *J Pediatr Gastroenterol Nutr.* 1996;22(1):17-37.
- 332 9. World Health Organization. Guideline: Updates on the management of severe acute
333 malnutrition in infants and children. Geneva,
334 http://apps.who.int/iris/bitstream/handle/10665/95584/9789241506328_eng.pdf?sequence=12013.
- 335 10. World Health Organization. Supplementary foods for the management of moderate acute
336 malnutrition in infants and children 6-59 months of age. Geneva,
337 [https://apps.who.int/iris/bitstream/handle/10665/75836/9789241504423_eng.pdf;jsessionid=3A36B5BF0](https://apps.who.int/iris/bitstream/handle/10665/75836/9789241504423_eng.pdf;jsessionid=3A36B5BF06457A30B54A52271447B6E7?sequence=12012)
338 [6457A30B54A52271447B6E7?sequence=12012](https://apps.who.int/iris/bitstream/handle/10665/75836/9789241504423_eng.pdf;jsessionid=3A36B5BF06457A30B54A52271447B6E7?sequence=12012).
- 339 11. Sarker SA, Ahmed T, Brussow H. Persistent diarrhea: a persistent infection with
340 enteropathogens or a gut commensal dysbiosis? *Environ Microbiol.* 2017;19(10):3789-801.
- 341 12. World Health Organization. Pocket book of hospital care for children: Guidelines for the
342 management of common childhood illnesses. Geneva,
343 https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/2013.
- 344 13. Rabbani GH, Larson CP, Islam R, Saha UR, Kabir A. Green banana-supplemented diet in the
345 home management of acute and prolonged diarrhoea in children: a community-based trial in rural
346 Bangladesh. *Trop Med Int Health.* 2010;15(10):1132-9.
- 347 14. Rollins NC, van den Broeck J, Kindra G, Pent M, Kasambira T, Bennish ML. The effect of
348 nutritional support on weight gain of HIV-infected children with prolonged diarrhoea. *Acta Paediatr.*
349 2007;96(1):62-8.
- 350 15. Valentiner-Branth P, H. Steinsland, G. Santos, M. Perch, K. Begtrup, M. K. Bhan, F. Dias, P. Aaby,
351 P., H. Sommerfelt, and K. Mølbak. A randomized controlled trial of dietary management of children with
352 persistent diarrhoea: sustained beneficial effect on ponderal and linear growth. *Am J Clin Nutr.*
353 2001;73:968-74.
- 354 16. Giannattasio A, Guarino A, Lo Vecchio A. Management of children with prolonged diarrhea.
355 *F1000Res.* 2016;5.
- 356 17. Karim AS, Akhter S, Rahman MA, Nazir MF. Risk factors of persistent diarrhea in children below
357 five years of age. *Indian J Gastroenterol.* 2001;20(2):59-61.
- 358 18. Deivanayagam N, Mala N, Ashok TP, Ratnam SR, Sankaranarayanan VS. Risk factors for
359 persistent diarrhea among children under 2 years of age. Case control study. *Indian Pediatr.* 1993;30(2):177-
360 85.

- 361 19. Sodemann M, Jakobsen MS, Molbak K, Martins C, Aaby P. Episode-specific risk factors for
362 progression of acute diarrhoea to persistent diarrhoea in west African children. *Trans R Soc Trop Med Hyg.*
363 1999;93(1):65-8.
- 364 20. Strand TA, Sharma PR, Gjessing HK, Ulak M, Chandyo RK, Adhikari RK, et al. Risk factors for
365 extended duration of acute diarrhea in young children. *PLoS One.* 2012;7(5):e36436.
- 366 21. QGIS. QGIS Development Team. QGIS Geographic Information System. Open Source
367 Geospatial Foundation Project. . 2.18 ed. <http://qgis.org2016>.
- 368 22. ArcGIS, ajhethiopia, cartographers. Kebeles for all regions except Somalia.
369 <http://www.arcgis.com/home/item.html?id=53807e932922445abc36c1f25c66e18b>, Downloaded March
370 2017: ArcGIS Online; 2015.
- 371 23. Google Inc. Google Earth In: 7.1.5.1557 V, editor.
372 <https://www.google.com/earth/download/gep/agree.html>: Google; 2015.
- 373 24. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards:
374 Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age:
375 Methods and development. . Geneva: World Health Organization; 2006
- 376 25. Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH, van EA, et al. The Global Enteric
377 Multicenter Study (GEMS) of diarrheal disease in infants and young children in developing countries:
378 epidemiologic and clinical methods of the case/control study. *Clin Infect Dis.* 2012;55 Suppl 4:S232-S45.
- 379 26. Psaki SR, Seidman JC, Miller M, Gottlieb M, Bhutta ZA, Ahmed T, et al. Measuring
380 socioeconomic status in multicountry studies: results from the eight-country MAL-ED study. *Popul Health
381 Metr.* 2014;12(1):8.
- 382 27. Bandsma RHJ, Sadiq K, Bhutta ZA. Persistent diarrhoea: current knowledge and novel
383 concepts. *Paediatr Int Child Health.* 2018:1-7.
- 384 28. Alam NH, Faruque AS, Dewan N, Sarker SA, Fuchs GJ. Characteristics of children hospitalized
385 with severe dehydration and persistent diarrhoea in Bangladesh. *J Health Popul Nutr.* 2001;19(1):18-24.
- 386 29. Bhutta ZA, Nelson EA, Lee WS, Tarr PI, Zablach R, Phua KB, et al. Recent advances and evidence
387 gaps in persistent diarrhea. *J Pediatr Gastroenterol Nutr.* 2008;47(2):260-5.
- 388 30. Islam SB, Ahmed T, Mahfuz M, Mostafa I, Alam MA, Saqeeb KN, et al. The management of
389 persistent diarrhoea at Dhaka Hospital of the International Centre for Diarrhoeal Disease and Research: a
390 clinical chart review. *Paediatr Int Child Health.* 2018;38(2):87-96.
- 391 31. Iannotti LL, Trehan I, Clitheroe KL, Manary MJ. Diagnosis and treatment of severely
392 malnourished children with diarrhoea. *J Paediatr Child Health.* 2015;51(4):387-95.
- 393 32. Platts-Mills JA, Babji S, Bodhidatta L, Gratz J, Haque R, Havt A, et al. Pathogen-specific burdens
394 of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). *Lancet Glob Health.*
395 2015;3(9):e564-e75.
- 396 33. Liu J, Platts-Mills JA, Juma J, Kabir F, Nkeze J, Okoi C, et al. Use of quantitative molecular
397 diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study.
398 *Lancet.* 2016;388(10051):1291-301.
- 399 34. Lazzarini M, Wanzira H. Oral zinc for treating diarrhoea in children. *Cochrane Database Syst
400 Rev.* 2016;12:CD005436.
- 401 35. Institute for Health Metrics and Evaluation HDN, The World Bank. . The Global Burden of
402 Disease: Generating Evidence, Guiding Policy – Sub-Saharan Africa Regional Edition.
403 [http://www.healthdata.org/policy-report/global-burden-disease-generating-evidence-guiding-policy-
404 %E2%80%93-sub-saharan-africa-regional](http://www.healthdata.org/policy-report/global-burden-disease-generating-evidence-guiding-policy-%E2%80%93-sub-saharan-africa-regional): Seattle, WA: IHME; 2013.
- 405 36. Das SK, Faruque AS, Chisti MJ, Malek MA, Salam MA, Sack DA. Changing trend of persistent
406 diarrhoea in young children over two decades: observations from a large diarrhoeal disease hospital in
407 Bangladesh. *Acta Paediatr.* 2012;101(10):e452-e7.

409 **Figure 1:** Flow diagram

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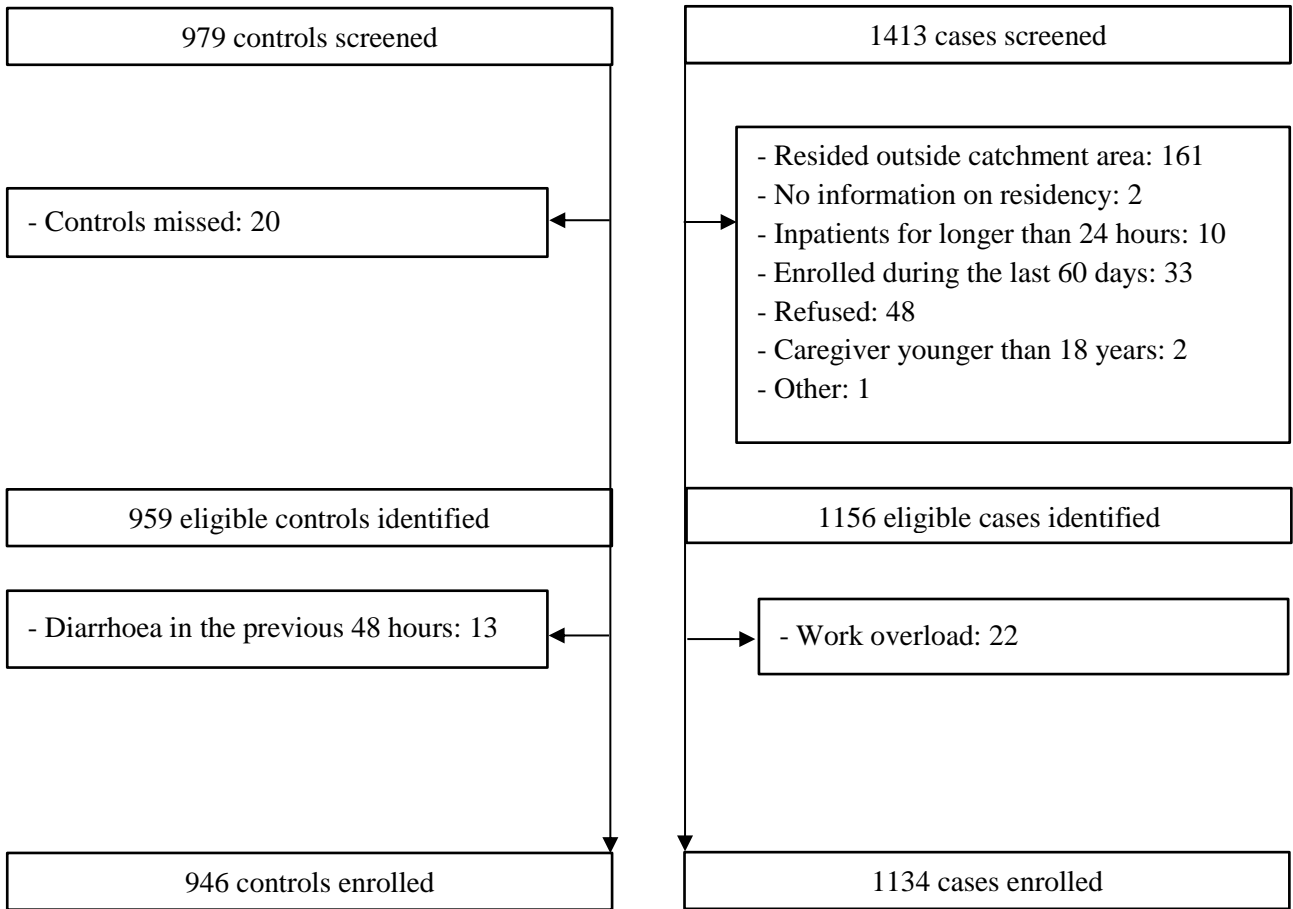
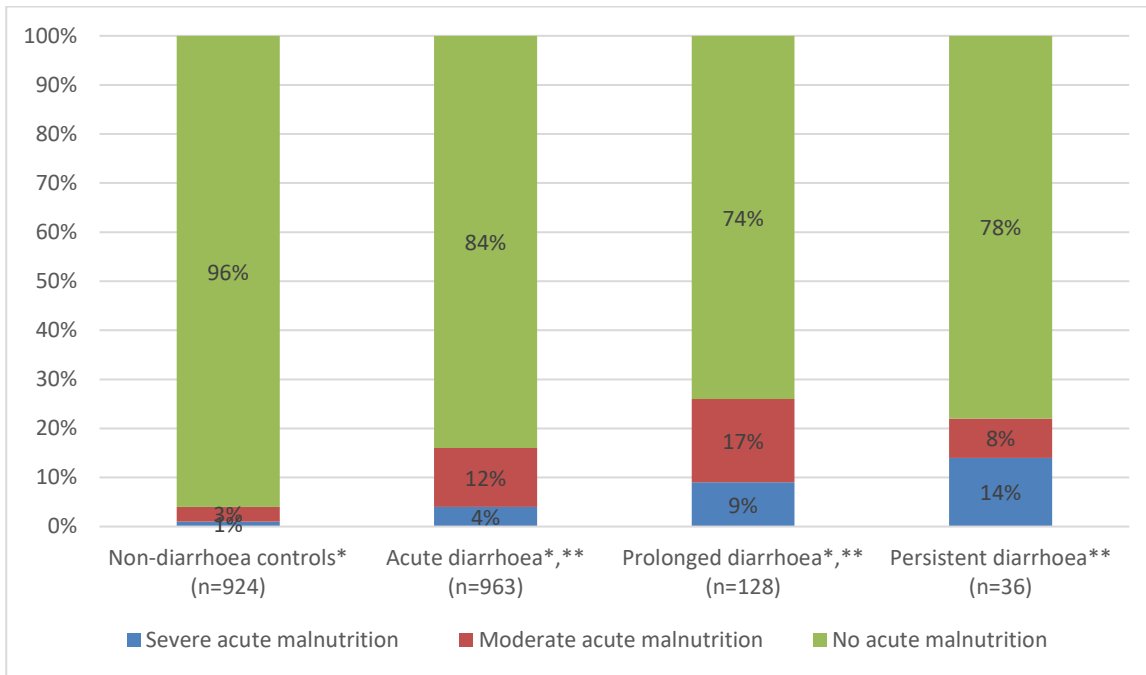


Figure 2: Proportion of children with acute malnutrition by duration of diarrhoea



** Twenty-two controls and seven cases had missing anthropometric data

* Proportion of children with MAM or SAM among children with any form of diarrhoea differed significantly from controls ($p < 0.0001$). Proportion of children with MAM or SAM among children with prolonged diarrhoea differed significantly from cases with acute diarrhoea ($p = 0.006$)

Table 1: Associations between demographic/clinical characteristics and diarrhoea based on 1134 cases and 946 controls given as ORs with 95% confidence intervals (95%CI)

	Non-diarrhoea controls	Cases	Adjusted OR ¹ (95% CI)
Number of children	946	1134	
Female sex, n (%)	439 (47%)	491 (43%)	0.86 (0.71, 1.05)
Age, months, mean (sd)	17.8 (±12.6)	16.6 (±11.7)	0.99 (0.99, 1.00)
Mid-upper arm circumference ≤125 mm for >6 months, n (%)	18 (2%)	104 (10%)	4.58 (2.64, 7.97)
Exclusive breastfeeding for <6 months, n (%)	332 (38%)	413 (39%)	1.06 (0.86, 1.30)
Born prematurely, n (%)	17 (1.8%)	64 (5.7%)	2.33 (1.27, 4.28)
WAM ² index < 0.50, n (%)	523 (57%)	538 (49%)	0.80 (0.66, 0.98)
Antibiotic use in previous week, n (%)	70 (7.5%)	116 (10.6%)	1.25 (0.86, 1.80)
Health facility visit in previous month, n (%)	238 (25%)	406 (36%)	1.43 (1.14, 1.79)
Admission to health facility, n (%)	78 (8.3%)	107 (9.5%)	1.05 (0.74, 1.50)
Previous treatment for malnutrition, n (%)	11 (1.2%)	19 (1.7%)	0.78 (0.33, 1.83)

¹ Adjusted for age and with random effects for enrolment month. District of residency excluded due to challenges with convergence of the statistical model

² Water/sanitation, Assets and Maternal education

Table 2: Association between demographic/clinical characteristics and prolonged or persistent diarrhoea (ProPD) based on 165 cases of ProPD and 967 cases with acute diarrhoea (AD) given as ORs with 95% confidence intervals (95%CI)¹

	AD	ProPD	Adjusted OR ² (95% CI)
Number of children	967	165	
Female sex, n (%)	422 (44%)	68 (41%)	0.81 (0.50, 1.30)
Age, months, mean (sd)	16.9 (\pm 11.8)	15.0 (\pm 11.4)	0.99 (0.97, 1.02)
Mid-upper arm circumference \leq 125 mm for >6 months, n (%)	78 (9%)	26 (19%)	2.10 (1.05, 4.22)
Stunting, n (%)	184 (19%)	45 (27%)	1.99 (1.16, 3.42)
Exclusive breastfeeding, <6 months, n (%)	342 (38%)	70 (46%)	1.04 (0.64, 1.69)
Born prematurely, n (%)	55 (6%)	9 (6%)	0.41 (0.13, 1.29)
WAM ³ index, < 0.50, n (%)	470 (50%)	68 (43%)	1.18 (0.70, 1.98)
Rotavirus vaccinated, n (%)	915 (95%)	150 (91%)	2.68 (0.50, 14.37)
History of vomiting, n (%)	563 (58%)	80 (48%)	0.63 (0.39, 1.02)
History of fever, n (%)	425 (44%)	67 (41%)	0.92 (0.56, 1.49)
Fever, measured, n (%)	144 (15%)	13 (8%)	0.45 (0.20, 1.04)
Antibiotic use in previous week, n (%)	78 (8%)	38 (24%)	1.45 (0.72, 2.91)
Zinc use in previous week, n (%)	57 (6%)	41 (25%)	3.49 (1.71, 7.12)
Primary reason for visit not diarrhoea, n (%)	117 (14%)	18 (13%)	1.04 (0.50, 2.15)
Health facility visit in previous month, n (%)	331 (34%)	74 (45%)	1.59 (0.98, 2.58)
Admission to health facility, n (%)	89 (9%)	17 (10%)	0.67 (0.29, 1.53)
Previous treatment for malnutrition, n (%)	14 (1%)	5 (3%)	0.96 (0.18, 5.21)
Moderate to severe diarrhoea, n (%)	158 (19%)	38 (26%)	1.13 (0.59, 2.15)
Stool characteristics			
Stool frequency per day, \geq 5, n (%)	374 (39%)	82 (50%)	1.23 (0.77, 1.99)
Watery stool, n (%)	183 (19%)	32 (20%)	0.76 (0.42, 1.39)

¹ Five cases had missing information on duration of diarrhoea

² Adjusted for age and with random effects for district of residency and enrolment month

³ Water/sanitation, Assets and Maternal education

Table 3: Existing general syndromic management recommendations by duration of diarrhoea and divided into degrees of acute malnutrition, highlighting the present knowledge gaps

	Acute diarrhoea	Prolonged diarrhoea	Persistent diarrhoea
No acute malnutrition	Zinc supplementation and rehydration when needed (1)	No specific recommendations, currently treated as acute diarrhoea.	Lactose reduced nutritional therapy and antibiotics and rehydration when needed (12)
		<i>Clinical trials needed</i>	<i>A simpler intervention and clinical trials needed</i>
Moderate acute malnutrition (MAM)	No specific recommendations besides nutritional supplementation (10) and rehydration for acute diarrhoea (1).	No specific recommendations besides nutritional supplementation (10) and rehydration as for acute diarrhoea (1).	No specific recommendations besides nutritional supplementation (10) and/or lactose reduced nutritional therapy and antibiotics and rehydration when needed (12).
	<i>Clinical trials needed</i>	<i>Clinical trials needed</i>	<i>Clinical trials needed</i>
Severe acute malnutrition (SAM)	Nutritional therapy, antibiotics, rehydration when needed (9).	Nutritional therapy, antibiotics, rehydration when needed (9).	Nutritional therapy, antibiotics, rehydration when needed (9).
	<i>Clinical trials needed</i>	<i>Clinical trials needed</i>	<i>Clinical trials needed</i>