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

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Abstract

Objectives

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

Methods

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

Results

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

Conclusions

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

Introduction

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

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

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

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

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

Methods

Study design and participants

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

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

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

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

Data collection

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

Definitions

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

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

Statistical methods

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

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

Ethical issues

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

Results

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

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

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

Factors associated with any diarrhoea

In the adjusted analysis we found that MUAC ≤125 mm (OR 4.58, 95%CI 2.64, 7.97), being born prematurely (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, 1.79) was associated with having diarrhoea (table 1). A low WAM index was negatively correlated with diarrhoea (OR 0.80, 95%CI 0.66, 0.98). Taking re-enrolment into account had negligible effect on the estimates. HIV status/exposure was not included in the model due to low prevalence. Interactions with age group (age < 12 vs ≥ 12 months), defined as heterogeneity of ORs were found for the following variables; 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 (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 0.45 (0.34, 0.58)).

AD compared with ProPD

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

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-enrolment into account made little difference to these estimates.

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

Conclusion

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

Author contributions

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

Declaration of interests

We declare no competing interests.

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Role of the funding source

The funders had no role in the design, data collection, data analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figure 1: Flow diagram

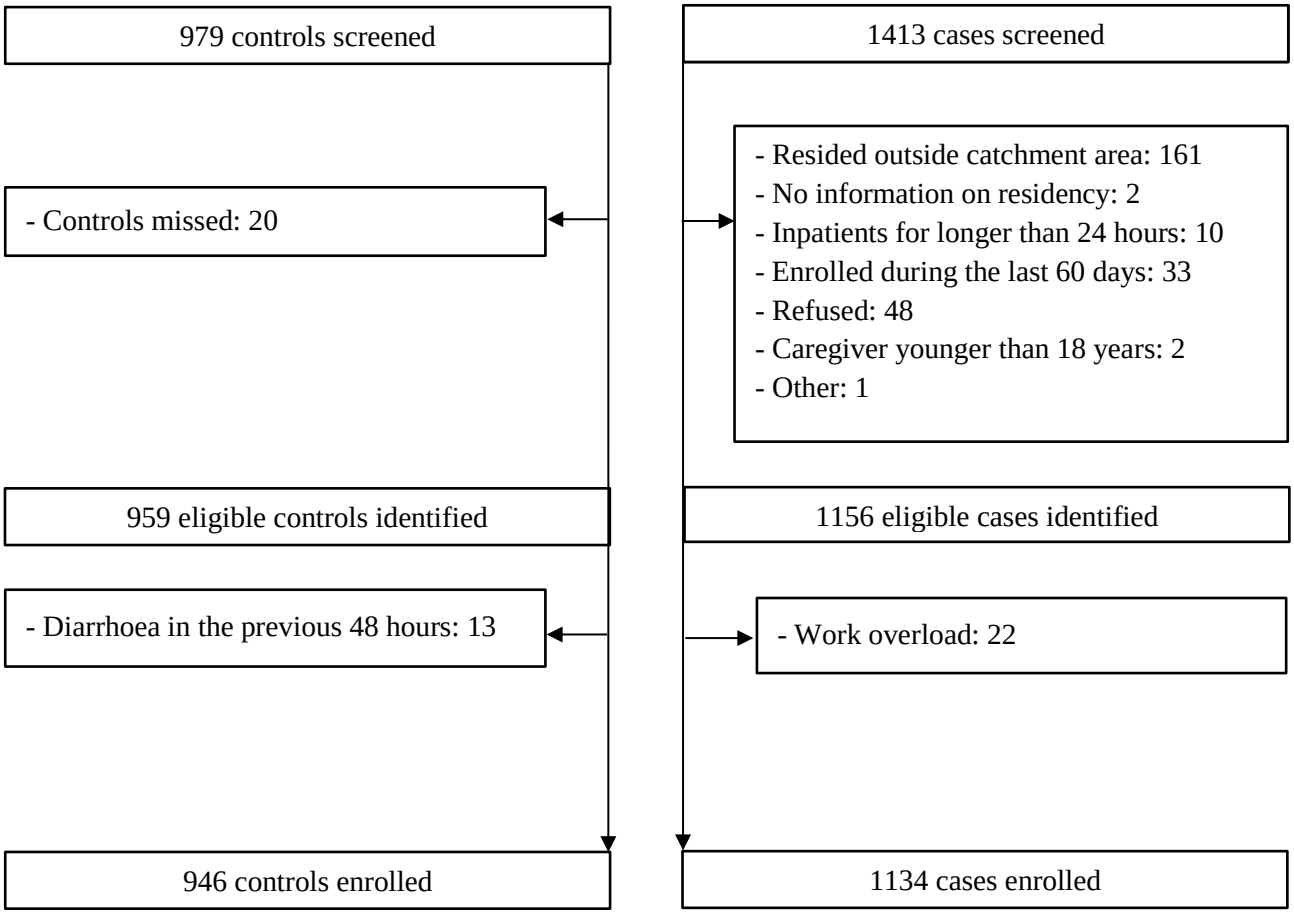
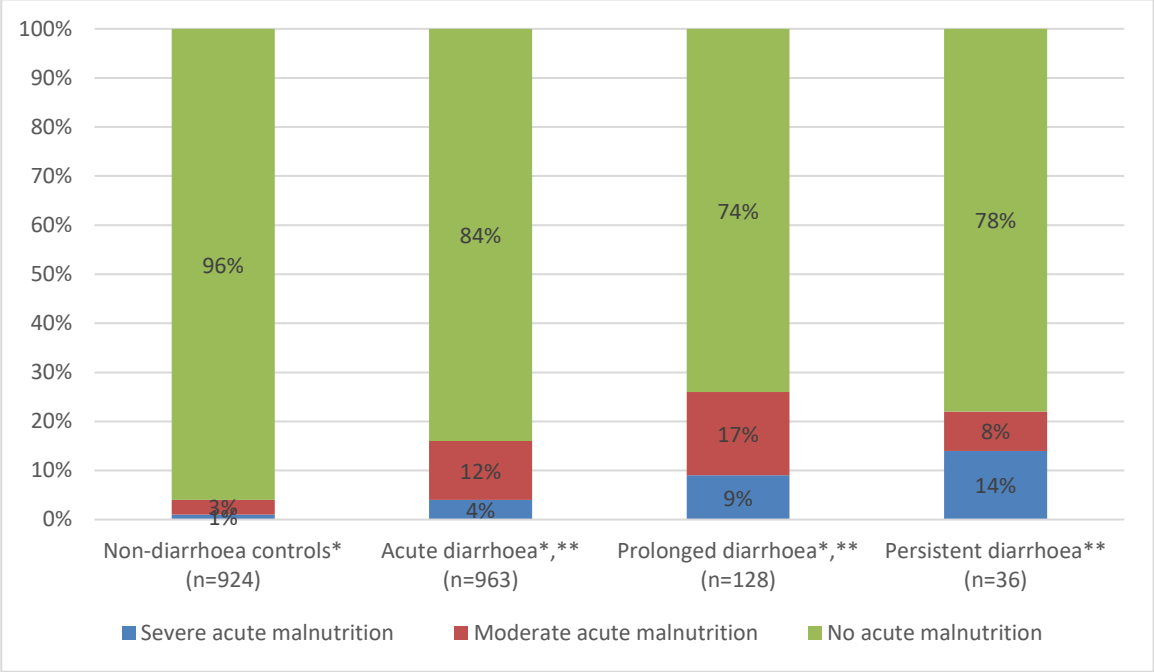


Figure 2: Proportion of children with acute malnutrition by duration of diarrhoea



** 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 (±11.8)	15.0 (±11.4)	0.99 (0.97, 1.02)
Mid-upper arm circumference ≤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, ≥ 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. *Clinical trials needed*	Lactose reduced nutritional therapy and antibiotics and rehydration when needed (12) *A simpler intervention and clinical trials needed*
Moderate acute malnutrition (MAM)	No specific recommendations besides nutritional supplementation (10) and rehydration for acute diarrhoea (1). *Clinical trials needed*	No specific recommendations besides nutritional supplementation (10) and rehydration as for acute diarrhoea (1). *Clinical trials needed*	No specific recommendations besides nutritional supplementation (10) and/or lactose reduced nutritional therapy and antibiotics and rehydration when needed (12). *Clinical trials needed*
Severe acute malnutrition (SAM)	Nutritional therapy, antibiotics, rehydration when needed (9). *Clinical trials needed*	Nutritional therapy, antibiotics, rehydration when needed (9). *Clinical trials needed*	Nutritional therapy, antibiotics, rehydration when needed (9). *Clinical trials needed*