Epidemiology and burden of *Cryptosporidium* diarrheal diseases in under five children in three sub-Saharan African countries, 2015-2018

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Background

- *Cryptosporidium* is associated with 88 million global diarrhoeal episodes among children <5 years and 48,000 under 5 deaths per year, 88% of these deaths are in Sub-Saharan Africa (1, 2).
- *Cryptosporidium* is the third most common cause of moderate-to-severe diarrhea (MSD) in children <5 years in low-income countries (3).
- The Vaccine Impact on Diarrhea in Africa (VIDA) study is a 36-month case-control study, which takes place in The Gambia, Mali and Kenya, following rotavirus (RV) vaccine introduction.
- Here, we present the epidemiology of *Cryptosporidium* in an endemic setting, post-RV vaccine introduction.

Objectives

- Assess MSD cases attributed to C*ryptosporidium* in children less than 5 years old.
- Assess the severity and clinical presentation of *Cryptosporidium* associated MSD and compare it to that of Rotavirus and other attributed watery diarrhea.
- Assess the temporal trend of *Cryptosporidium* attributed MSD cases.

Methods

Data collection

- VIDA enrolment began in May 2015 (July 2015 for Kenya).
- MSD cases were enrolled in 3 age strata (0-11, 12-23, 24-59 months) from Sentinel Health Centres within the demographic surveillance system (DSS).
- 1-3 diarrhea-free controls were enrolled within 2 weeks of the case and were matched on age, gender, and residential area.
- Demographic, epidemiological, and clinical information were collected from each participant.
- Height/length, weight, and mid-upper arm circumference (MUAC) were measured at enrollment.
- At least 4 grams of stool was collected at enrollment.

Laboratory testing

- TaqMan Array Card (TAC)-quantitative polymerase chain reaction (qPCR) used to detect 26 enteropathogens, including the 18S rRNA gene of *Cryptosporidium* species.
- Quantification cycle (Cq) values <35 indicate pathogen presence (a positive result).

Data analysis

- The episode specific attributable fraction (AFe) for each case child was estimated using the odds ratio from an adjusted conditional logistic regression.
- Etiologic detection: When the AFe was ≥ 0.5 for a particular pathogen it was assumed that the child's episode was attributed to this pathogen. These are described as attributable cases.
- Chi-squared tests of significance were used to compare categorical variables.
- The weighted(be age group and site) number *Cryptosporidium* etiologic and non-etiologic cases were used when assessing seasonality.

Results

- A total of 4765 cases and 4775 controls were tested by qPCR for *Cryptosporidium*. Off them, 1106 (23.2%) cases and 873 (18.3%) controls were positive for *Cryptosporidium*.
- At all sites and in all age groups, *Cryptosporidium* was more commonly detected in MSD cases than controls (Table 1).
- Etiologic detections of *Cryptosporidium* were more common among infants and toddlers compared to older age group at all three sites and were highest in The Gambia compared to Mali and Kenya (Table 1).
- *Cryptosporidium*-attributed cases were less severe overall (modified Vesikari score p <0.001) compared to RV-attributed cases (Table 2).
- *Cryptosporidium*-associated cases experienced more prolonged diarrhea than RV and all other attributed cases of watery diarrhea (p <0.001 for both) (Table 2).
- *Cryptosporidium*-attributed MSD cases were more likely to have severe acute malnutrition (MUAC <11.5 cm) at the time of enrollment than RV-attributed cases and all other attributed cases of watery diarrhea (P<0.001 for both) (Table 2).
- *Cryptosporidium*-attributed MSD in The Gambia and Mali displayed strong seasonal peaks which coincided with the highest rainfall, but clear annual trends were not observed in Kenya (Figure 1).
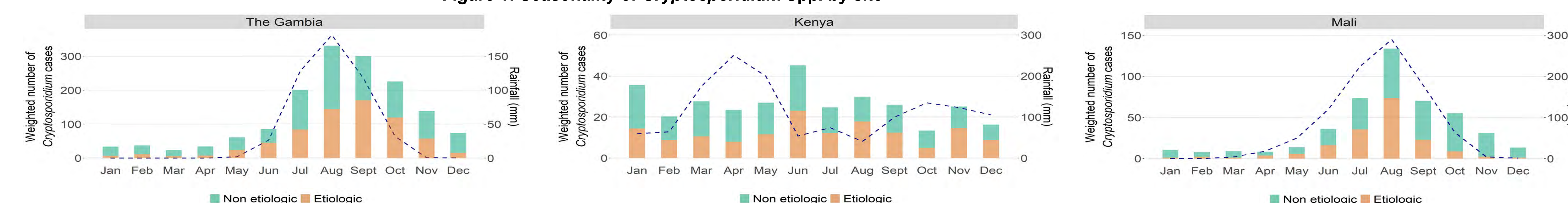
Table 1: Detection of Cryptosporidium by qPCR from VIDA enrolees, by age group & sites

	The Gambia		Mali		Kenya	
	Case	Control	Case	Control	Case	Control
0-11 months						
QPCR result	N = 524	N = 526	N = 592	N = 591	N = 581	N = 577
Positive n (%)	170 (32.4)	127 (24.1)	155 (26.2)	124 (21.0)	80 (13.8)	80 (13.8)
Etiologic detection n (%)	88 (16.8)		83 (14.0)		43 (7.4)	
12-23 months						
QPCR result	N = 598	N = 607	N = 547	N = 547	N = 518	N = 517
Positive n (%)	166 (27.8)	157 (25.9)	141 (25.8)	108 (19.7)	115 (22.2)	70 (13.5)
Etiologic detection n (%)	72 (12.0)		38 (6.9)		52 (10.0)	
24-59 months						
QPCR result	N = 511	N = 515	N = 461	N = 460	N = 433	N = 435
Positive n (%)	145 (28.4)	116 (22.5)	85 (18.4)	72 (15.7)	49 (11.3)	32 (7.4)
Etiologic detection n (%)	46 (9.0)		18 (3.9)		20 (4.6)	

Table 2: Clinical presentation of attributed *Cryptosporidium*, rotavirus and non-*Cryptosporidium* watery diarrhoea among VIDA cases

Clinical presentation		Points	*Cryp* attributed MSD n = 450	RV attributed MSD n = 598	C*ryp* vs. RV p-value	Watery non-*Cryp* attributed n = 1,928	C*ryp* vs. Watery non-*Cryp* p-value
Vesikari score							
	Mild	<7	55 (12.2%)	55 (9.2%)		261 (13.5%)	
	Moderate	7-10	180 (40.0%)	181 (30.3%)	<0.001	748 (38.8%)	0.753
	Severe	>= 11	215 (47.8%)	361 (60.4%)		916 (47.5%)	
	Median (IQR)	N/A	10 (8, 13)	11 (9, 13)	<0.001	10 (8, 12)	0.948
Vesikari score components							
	1-3	1	99 (22.0%)	96 (16.1%)		348 (19.1%)	
Max number of stools per day	4-5	2	277 (61.6%)	361 (60.4%)	0.004	1159 (60.1%)	0.076
	>= 6	3	74 (16.4%)	141 (23.6%)		401 (20.8%)	
	1-4	1	139 (30.9%)	256 (42.8%)		816 (42.3%)	
Duration of diarrhea (days)	5	2	71 (15.8%)	108 (18.1%)	<0.001	266 (13.8%)	<0.001
	>= 6	3	240 (53.3%)	234 (39.1%)		846 (43.9%)	
Max no. of vomiting episodes on worst day, if experienced vomiting	1	1	42 (16.3%)	43 (9.2%)		176 (15.1%)	
	2-4	2	191 (74.0%)	325 (69.7%)	<0.001	812 (69.8%)	0.077
	>=5	3	25 (9.7%)	98 (21.0%)		176 (15.1%)	
	1	1	54 (20.9%)	109 (23.4%)		350 (30.1%)	
Vomiting duration (days)	2	2	108 (41.9%)	214 (45.9%)	0.202	510 (43.9%)	<0.001
	>= 3	3	96 (37.2%)	143 (30.7%)		303 (26.1%)	
Dehydration	Some	2	369 (87.9%)	470 (84.1%)	0.114	1506 (81.8%)	0.004
	Severe	3	51 (12.1%)	89 (15.9%)		335 (18.2%)	
Other clinical presentations							
Blood in stool	Yes		48 (10.7%)	43 (7.2%)	0.062	-	-
Stunted at enrollment (HAZ < -2)	Yes		104 (23.1%)	112 (18.7%)	0.097	450 (23.3%)	0.967
Malnutrition at enrollment	None		349 (77.6%)	510 (85.3%)		1,637 (84.9%)	
MUAC 11.5-12.5 cm	Moderate		66 (14.7%)	72 (12.0%)	<0.001	228 (11.8%)	<0.001
MUAC <11.5 cm	Severe		35 (7.8%)	16 (2.7%)		63 (3.3%)	

Figure 1: Seasonality of *Cryptosporidium* Spp. by site

Conclusion

- *Cryptosporidium* spp. is predominant pathogens after introduction of RV vaccine in younger children.
- *Cryptosporidium*-attributed MSD cases were less severe overall (modified Vesikari score) compared to RV-attributed cases and experienced a prolonged duration of diarrheal episode.
- *Cryptosporidium*-attributed MSD cases were more likely associated with malnutrition compared to RV-attributed cases & other attributed watery diarrhea.
- *Cryptosporidium*-attributed MSD displayed a strong seasonal peak which coincided with the rainy season in The Gambia and Mali.

References

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Vaccine Impact on Diarrhea in Africa

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