Title: Film Array Gastrointestinal Panel Compared to Usual Care for ED Evaluation of Infectious Diarrhea

"RCT of GIP in ED for ID"
or "RAPID"

ClinicalTrials.gov Identifier: NCT03809117

Interim Report

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Prepared by the Section on Clinical Research
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Introduction

This report describes the work undertaken by the investigators for the "Film Array Gastrointestinal Panel Compared to Usual Care for ED Evaluation of Infectious Diarrhea study" also known as RCT of GIP for ID in ED or "*RAPID*." The single-center study was performed at the George Washington University Medical Center (GWU). The principal investigator for this study is Dr. Andrew Meltzer.

Background

For patients presenting to the emergency department (ED), real-time treatment decisions are predicated on rapid and accurate diagnosis. In the case of infectious diarrhea, traditional diagnostic tests have a low sensitivity and a long processing time and therefore are not useful in the ED for real-time treatment decisions. As such, physicians must treat diarrheal infection based on history of recent travel and high-risk clinical features. Rapid diagnosis and targeted treatment have only recently become possible with the introduction of multiplex polymerase chain reaction (PCR) panels that identify bacteria, viruses, and protozoa during a single ED visit. In this study, we aimed to determine if a rapid multiplex PCR test can lead to a more appropriate utilization of antibiotics for ED patients with infectious diarrhea.

Gastrointestinal illness accounts for millions of cases per year in the US and results in approximately 500,000 hospitalizations and 5000 deaths.[1] In general, the infectious agent is not identified. Norovirus and salmonella species are believed to account for 5.5 and 1.0 million cases each year, respectively, and are the most commonly identified agents.[2] The traditional stool culture is limited by time delay to results and low yield for identifying the cause of infectious diarrhea. In six studies conducted between 1980 and 1997, the diagnostic yield of stool cultures ranged from 1.5 to 5.6 percent with a high cost to find a single positive.[3] For admitted patients, the yield decreases over the hospital stay to 0.5% after 72 hours.[3] Distinguishing viral causes from bacterial and protozoal causes is crucial because antibiotic treatment can reduce the severity of symptoms and the risk of future spread.[3,4,5]

Unfortunately, clinical findings may not be predictive of bacterial source. For example, neither bloody nor persistent diarrhea are associated with positive stool culture.[6] Typically, epidemiological risk factors serve as cornerstone of treatment decisions - ACG guidelines recommend that testing should be based on history of travel. In the absence of travel, antibiotics for routine community acquired diarrhea are discouraged due to the likelihood of viral etiology such as norovirus, rotavirus, and adenovirus.[7]

Introduction of the rapid testing panels increases the identification of treatable pathogens in the ED and may improve our ability to provide infection control.[8,9] A test-and-treat strategy is feasible in the ED setting and could benefit symptomatic patients with gastrointestinal complaints.[10] While there are several manufacturers with multiplex gastrointestinal testing panels, this study utilizes the FilmArray GI Panel which has a reported specificity of more than 95% for all panel targets.[11]

This interim report will summarize the progress of investigator-initiated randomized control trial: Film Array Gastrointestinal Panel Compared to Usual Care for ED Evaluation of Infectious Diarrhea (ClinicalTrials.gov Identifier: NCT03809117) conducted with a grant from Biomerieux, Inc.

History of the Study

The RAPID study began in November 17, 2018 as an investigator-initiated funded study awarded to Dr. Andrew Meltzer in the Department of Emergency Medicine at the George Washington University in Washington DC. The study sponsor is Biomerieux, Inc.

A randomized control design was initiated where clinically stable patients in the ED with suspected infectious diarrhea were randomized to receive a rapid Gastrointestinal Panel (GIP) study or standard of care (SOC). The primary question was whether the use of a rapid diagnostic testing strategy improved the number of ED patients with bacterial diarrhea who received antibiotics. Additionally, this study sought to determine if there was a decrease in the number of patients with viral diarrhea who received antibiotics. The hypothesis was grounded on the following assumptions:

- Antibiotics are generally recommended in patients with bacterial diarrhea and contraindicated for viral diarrhea.
- The clinical distinction between viral and bacterial diarrhea can be challenging.
- Accurate identification of the causative agent allows the clinician to target treatment for patients with bacterial causes.

The Biofire FilmArray GI Panel received U.S. Food and Drug Administration (FDA) 510(k) clearance for the FilmArray® Gastrointestinal (GI) Panel in May 2014. The test consists of automated nucleic acid extraction, reverse transcription, amplification, and analysis, with results available in 1 hour per run per specimen. The FilmArray GI Panel detects seven bacteria (*Aeromonas* spp., *Campylobacter* spp. [*C. jejuni*, *C. coli*, and *C. upsaliensis*], *C. difficile* toxin A/B, *P. shigelloides*, *Salmonella* spp., *Vibrio* spp. [*V. parahaemolyticus*, *V. vulnificus*, and *V. cholerae* with specific detection of *V. cholerae*], and *Y. enterocolitica*), six diarrheagenic *Shigella* spp./*E. coli* (enteroaggregative *E. coli* [EAEC], enteropathogenic *E. coli* [EPEC], enterotoxigenic *E. coli* [ETEC], enteroinvasive *E. coli* [EIEC]/*Shigella* spp., Shiga-like toxin-producing *E. coli* [STEC] [with specific detection of *E. coli* O157]), four parasites (*Cryptosporidium*, *Cyclospora cayetanensis*, *E. histolytica*, and *G. lamblia*), and five viruses (adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, and sapovirus). Each FilmArray GI Panel pouch contains an internal nucleic acid extraction control and a PCR control. The FilmArray GI Panel runs were considered valid if the run is completed normally and internal controls are passed. The FilmArray GI Panel software performs automated result analysis with each target in a valid run reported as detected or not detected.

The GW IRB approved the trial by a full board on June 1, 2018. Study was renewed on June 2019 and June 2020. Study was registered on clinicaltrials.gov on January 18, 2019. First patient was enrolled in November 17, 2018. In March 15, 2020 as the SARS-CoV-2 crises reached epidemic and subsequently pandemic levels, the study was put on hold. At this time, study investigators paused to perform an interim analysis and hold a full meeting regarding the next steps and modifications that need to be made moving forward.

Statistical Methods

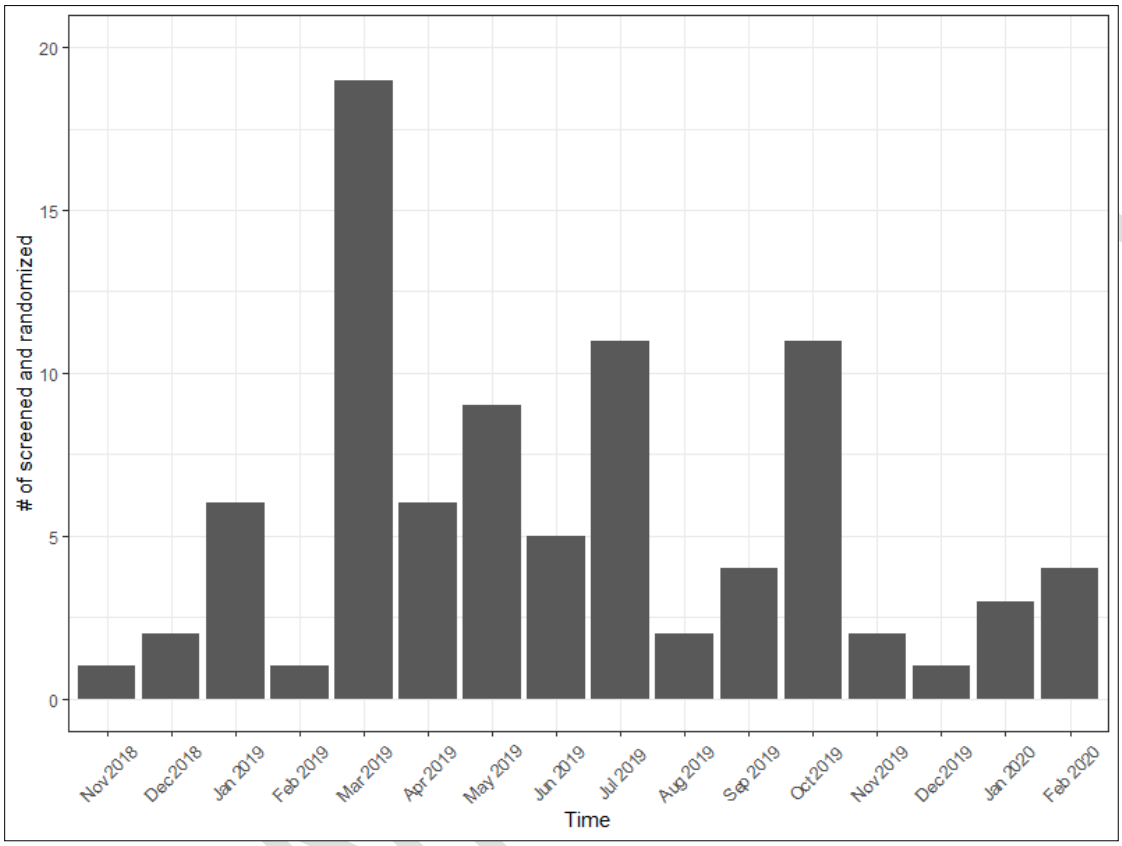
In this report, individual participants are denoted by their patient number, a unique identifier. In the tables, “N” refers to the number of observations with non-missing values for the variable. The p-values reported are nominal p-values. Unless otherwise specified, they are based on the usual chi-square statistic (or Fisher’s exact test in the case of infrequent outcomes) for discrete variables or the Wilcoxon Rank Sum test for continuous variables. Although data for some participants may be missing, all relevant data available from each participant will be employed in the analyses.

In planning this study, in order to detect a 20% improvement in appropriate antibiotics, we need 88 patients in each group to detect a difference of 80% versus 60% with 95% confidence and 80% power. The sample size was adjusted to take into consideration losses.

Recruitment

In the GW ER, there were 663 screenings. Figure 1 shows the 87 randomizations for the multi-center study by month and year.

Figure 1: Screening by month.



Screening Demographics

The demographics obtained for each screening are gender, race and ethnicity as shown below. Missing data was excluded.

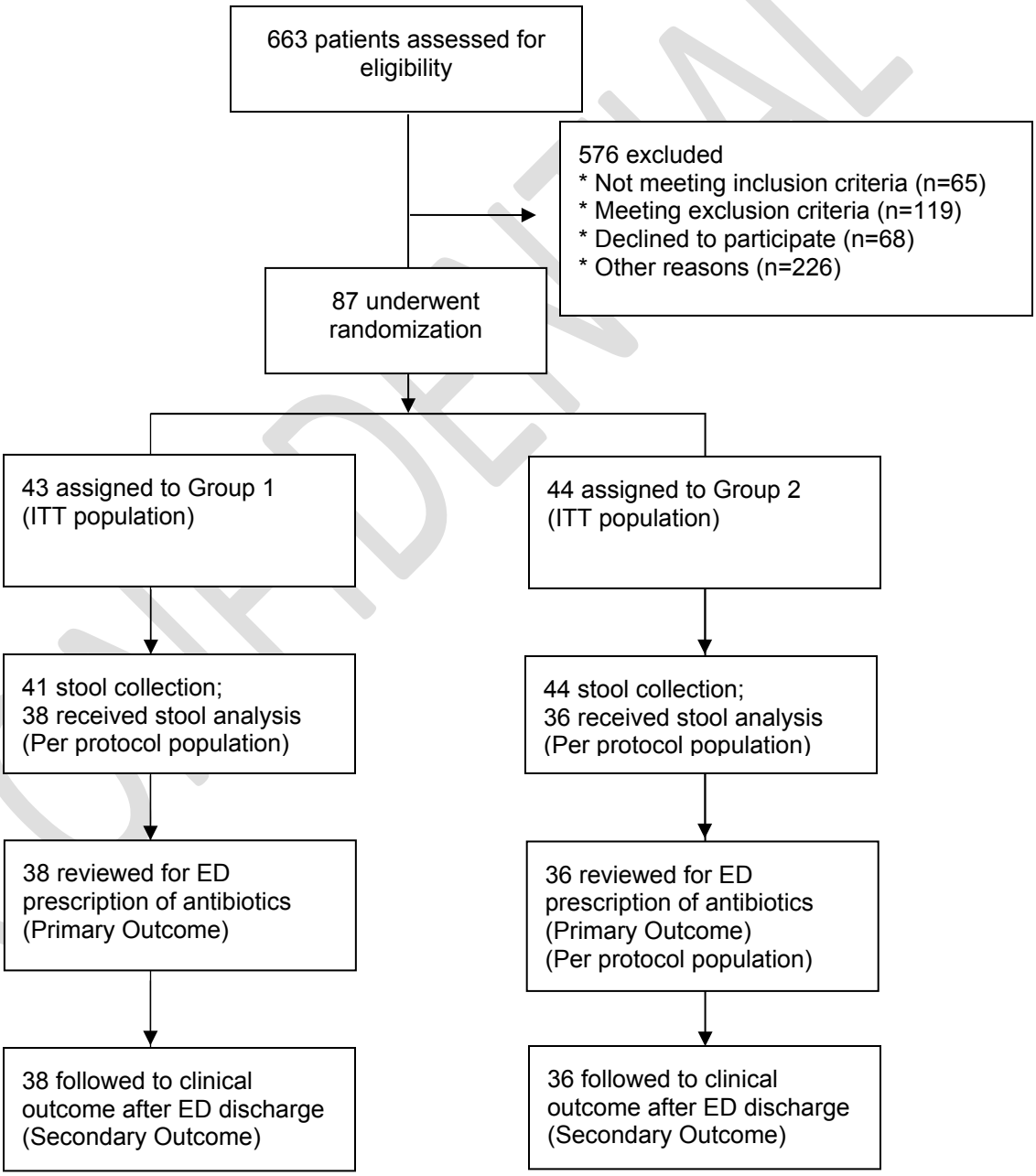
Table 1: Baseline characteristics of those who were screened.

Characteristic	**N**	**% Screened*** *(missing excluded)
Female	359	54%
Non-white race	126	19%
Hispanic	22	3%

Consort Diagram

A CONSORT diagram is shown in Figure 2. There were 663 screenings resulting in the 87 (13%) randomizations. Of the 663 screenings, there were 68 (12%) who declined to participate. Full list of exclusion is included in Table 2. The biggest single reason for exclusion was that a stool sample was not provided. Of the 87 randomized participants, only 76 patients provided stool samples and were randomized to either Group 1 or Group 2.

Figure 2: CONSORT Diagram



Reasons Ineligible

For patients who were excluded, the reasons for being excluded are presented in Table 2. A majority were excluded due to meeting multiple exclusion criteria.

Table 2: Reasons for Exclusion

Reason for Exclusion	Number of Patients
Record incomplete	8
Presumed non-infectious diarrhea	36
Inadequate clinical evidence	21
Chronic symptoms (>14 days)	49
Likely non-infectious cause of diarrhea (IBD, IBS, etc.)	41
Confirmed *Clostridium difficile* infection	7
Patient unable to consent	16
Inability to follow up	6
Refused to participate	68
Stool sample not provided	94
Multiple exclusion criteria met	226
Other	4

Baseline Characteristics

The full cohort of participants who provided stool for collection is shown below with the baseline characteristics by treatment group. The treatment groups are well-balanced with respect to characteristics at baseline.

Table 3: Baseline characteristics (n=87)

	Group 1 (n=43)	**Group 2 (n=44)**
Median Age at Screening (yr)	36	35
Female (%)	26 (60.5)	20 (45.5)
Black (%)	26 (66.7)	25 (62.5)
White (%)	10 (25.6)	12 (30.0)
Asian, Native American, Pacific Islander, Unknown (%)	3 (7.8)	3 (7.5)
Hispanic or Latino (%)	6 (14.6)	8 (19.5)
Not Hispanic or Latino (%)	35 (85.4)	33 (80.5)
Three or more loose stools in the past 24 hours (%)	41 (100.0)	44 (100.0)
Symptoms greater than 24 hours? (%)	33 (76.7)	33 (75.0)
Dehydration? (%)	30 (69.8)	25 (56.8)
Vomiting, reported by patient (%)	29 (67.4)	28 (63.6)
Abdominal Pain, reported by patient (%)	37 (86.0)	37 (84.1)
Fever, reported by patient (%)	15 (34.9)	16 (36.4)
Symptoms lasting more than 7 days? (%)	1 (2.3)	2 (4.5)
Heart Rate (bpm, median, at triage) *	93.00 [86.00, 105.00]	84.50 [75.50, 97.25]
Systolic Blood Pressure (mmHg, median, at triage) *	126.00 [117.50, 137.00]	132.50 [123.00, 147.25]
Temperature	98.20 [97.90, 98.60]	98.40 [98.05, 98.65]
Recent Travel (%)	9 (20.9)	14 (31.8)
Prescription antibiotics (%)	3 (7.0)	3 (6.8)

* P value< 0.05

Infection by Group

Table 4 summarizes the pathogens per group for all participants who had a stool sample analyzed.

Table 4: Summary of pathogen detected by GIP by type

	Group 1 (%) n=38	**Group 2 (%) n=36**
Campylobacter (%)	4 (10.5)	3 (8.3)
Clostridium difficile toxin A/B (%)	1 (2.7)	2 (5.7)
Plesiomonas shigelloides (%)	0	0
Salmonella (%)	1 (2.6)	2 (5.6)
Vibrio, non-cholerae (%)	1 (2.6)	0 (0.0)
Vibrio cholerae (%)	1 (2.6)	0 (0.0)
Yersinia enterocolitica (%)	0	0
Enteroaggregative E. Coli (EAEC) (%)	2 (5.3)	5 (13.9)
Enteropathogenic E. Coli (EPEC) (%)	3 (7.9)	6 (16.7)
Enterotoxigenic E. Coli (ETEC) (%)	2 (5.3)	1 (2.8)
Shiga-like toxin-producing E. Coli (STEC) stx1/stx2 (%)	0	0
Shigella/Enteroinvasive E. coli (EIEC) (%) *	5 (13.2)	0 (0.0)
Cryptosporidium (%)	0 (0.0)	2 (5.6)
Cyclospora cayetanensis (%)	0	0
Entamoeba histolytics (%)	0	0
Giardia lamblia (%)	1 (2.7)	0 (0.0)
Adenovirus 40/41 (%)	0 (0.0)	2 (5.6)
Astrovirus (%)	0 (0.0)	1 (2.8)
Norovirus GI/GII (%)	13 (34.2)	7 (19.4)
Rotavirus (%)	2 (5.3)	2 (5.6)
Sapovirus (%)	1 (2.6)	1 (2.8)

* P= 0.021

Infections were summarized by class of infectious agent as bacterial or protozoa or virus.

Table 5: Summary by class of infection per group

	Group 1 (%)	Group 2 (%)	Total
Bacteria	11 (28.9)	9 (25.0)	20
Bacteria + virus	3 (7.9)	2 (5.6)	5
Parasites	1 (2.6)	2 (5.6)	3
Not detected	11 (28.9)	13 (36.1)	24
Virus only	12 (31.6)	10 (27.8)	22
Total	38	36	74

Results / Outcomes

The primary clinical question is whether the use of PCR was associated with a change in management, specifically appropriate use of antibiotics as defined as antibiotics for bacteria or protozoa and not for virus. For all 74 patients who provided stool samples, a chart review was completed to assess ED management. Follow-up telephone contacts were also conducted for all participants and were attempted at post-randomization days 2, 7 and 30. (Table 6) Follow-up attempts were made at least four times with calls at different times before participant was considered lost to follow-up. No participants withdrew consent after the time of enrollment. Overall, attempted contacts were documented for 100% of those expected.

Enrollment and follow-up

Table 6: Participants reached for follow-up outcomes

	Group 1	Group 2	Total
Number Randomized	43	44	87
Number Analyzed	38	36	74
Number Reached at Day 2	30	25	55
Number Reached at Day 7	26	24	50
Number Reached at Day 30	32	36	68

ED Management

In table 7, we demonstrate, that patients in group 1 were more likely to receive antibiotics in the ED (p=0.021) for any cause.

Table 7: Summary of ED Management

7a: per protocol analysis

ED Management	**Group 1 (n =38)**	**Group 2 (n=36)**
Antibiotics given in ED for Diarrhea (Name, Dosage) (%)	10 (26.3)	3 (6.8)
Antibiotics Prescribed for Diarrhea (%)	13 (34.2)	8 (22.2)
IV Rehydration Therapy? (%) Lactated Ringers / Normal Saline	31 (81.6)	25 (69.4)
Antidiarrheal Medication Prescribed (%)	4 (10.5)	2 (5.7)
Admitted to Hospital	7(18.4)	3 (8.3)
Computed Tomography ordered (%)	8 (21.1)	8 (22.2)
Length of Stay (in hours) (median [IQR])	7.68 [6.43, 10.67]	8.15 [5.90, 11.23]

7b: ITT analysis (includes all patients randomized)

ED Management	**Group 1 (n = 43)**	**Group 2 (n = 44)**
Antibiotics given in ED for Diarrhea (Name, Dosage) (%) *	11 (25.6)	3 (6.8)
Antibiotics Prescribed for Diarrhea (%)	14 (32.6)	8 (18.2)
IV Rehydration Therapy? (%) Lactated Ringers / Normal Saline	34 (80.1)	31 (72.1)
Antidiarrheal Medication Prescribed (%)	4 (9.3)	3 (7.0)
Admitted to Hospital	8 (18.6)	3 (7.0)
Computed Tomography ordered (%)	10 (23.3)	8 (18.2)
Length of Stay (in hours) (median [IQR])	7.87 [6.45, 10.55]	8.15 [5.90, 10.76]

* p-value = 0.021

Antibiotics by Group

A primary question of the study is the appropriate use of antibiotics for bacterial diarrhea. In Group 1, antibiotics were given for 87% of patients with bacterial or protozoal infection versus Group 2 in which patients were given antibiotics in 46% of bacterial or protozoal infections. (Table 8)

Table 8: Antibiotics Administered for Diarrhea (ED or as Prescription)

	Group 1	**Group 2**
Antibiotics given for Bacterial or Protozoal Infection	13/15 0.87, (0.62. 0.96)	6/13 0.46, (0.23, 0.71)
Antibiotics Given for Viral Infection	1/12	1/10
Antibiotics given for None detected	3/11	2/13

Table 8a. Antibiotics given for any reason

	Group	1	2	p-value
n		38	36	
Antibiotics? (%)	No	21 (55.3)	27 (75.0)	0.125
	Yes	17 (44.7)	9 (25.0)	

Table 8b. Antibiotics given for Bacteria /Protozoa

	Group	1	2	p-value
n		15	13	
Antibiotics? (%)	No	2 (13.3)	7 (53.8)	0.042
	Yes	13 (86.7)	6 (46.2)	

Table 8c. Antibiotics given for viral infection

	Group	1	2	p-value
n		12	10	
Antibiotics? (%)	No	11 (91.7)	9 (90.0)	1
	Yes	1 (8.3)	1 (10.0)	

Table 8d. Antibiotics given for none detected

	Group	1	2	p-value
n		11	13	
Antibiotics? (%)	No	8 (72.7)	11 (84.6)	0.63
	Yes	3 (27.3)	2 (15.4)	

Without Bonferroni correction in multiple test, the test for Table 8b for antibiotics given for Bacteria /Protozoa is significant with p-value of 0.042. If you consider the Bonferroni correction, a new alpha-level = 0.05/3 = 0.0167 which is less than 0.042.

Follow-up Adherence and Compliance

In Table 9, we see a non-significant trend toward improved symptoms in group 1 versus group 2. (p-value 0.37)

Table 9: Follow-up for Symptoms

	Grp1	**Grp2**
Day2: Do you still have the same symptoms as when you came to the Emergency department? (%)	12 (41.4)	11 (50.0)
Day7: Do you still have the same symptoms as when you came to the Emergency department? (%)	2 (7.7)	4 (20.0)
Day30: Do you still have the same symptoms as when you came to the Emergency department? (%)	2 (6.2)	4 (14.8)
	16 (42%)	19 (53%)

In Table 10, we compared return visits for those in group 1 versus group 2. (p-value 0.51)

Table 10: Return to the ED

	Grp1	**Grp2**
Day2: Have you returned to any Emergency department for similar symptoms? (%)	0 (0.0)	0 (0.0)
Day7: Have you returned to any Emergency department for similar symptoms? (%)	0 (0.0)	1 (5.0)
Day30: Have you returned to any Emergency department for similar symptoms? (%)	1 (3.3)	1 (3.7)

Clinical differences between bacterial and viral infection

A model was created to determine if there were clinical or historical factors associated with bacterial infection.

Table 11: Logistic regression results after variable selection

Coefficient Estimate			
Parameter	**Estimate**	**Standard Error**	**P-value**
Intercept	-129.5	119.8	0.2797
Greater than or equal 2 days of diarrhea	2.8105	1.2762	0.0277
Vomiting	-6.1649	2.2979	0.0073
Fever	2.4230	1.2238	0.0477
Triage Pulse (bpm)	-0.1099	0.0561	0.0502
Triage sbp (mmHg)	-0.0878	0.0485	0.0702
SpO2 (%)	-0.6018	0.4361	0.1676
Temperature (Fahrenheit)	2.1561	1.2863	0.0937

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
When did this episode of diarrhea start? (2 days or greater) vs (Less than 24 hours ago)	16.618	1.362	202.728
Vomiting (Yes) vs (No)	0.002	<0.001	0.190
Fever (Yes) vs (No)	11.279	1.025	124.168
Triage Pulse (bpm)	0.896	0.803	1.000
Triage SBP (mmHg)	0.916	0.833	1.007
SpO2 (%)	0.548	0.233	1.288
Temperature (Fahrenheit)	8.638	0.694	107.471

Side Effects and Adverse Events

There were no adverse events reported for the study. For serious adverse events, the study employs the definition used by the FDA which is: death, life-threatening, hospitalization, disability, congenital anomaly, or other interventions. No reported events were considered serious per the above definition.

Protocol Deviations/ Adherence

There was one protocol deviation in study. The protocol deviation related to the plan to get additional consent from participants to keep samples for future studies. Unfortunately, due to miscommunication with staff, most participants were not asked to specifically sign the additional question on the consent form. As a result, we were forced to destroy most of the samples. This deviation had no effect on the current study and only affects opportunities to do future additional studies.

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