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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

FINAL REPORT

THE MAPSAN TRIAL
A controlled, before-and-after trial of an urban sanitation intervention to reduce enteric infections in children

June 2017

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Abbreviations

CDC	*Centers for Disease Control and Prevention*
BMGF	*Bill and Melinda Gates Foundation*
GPP	*Gastrointestinal Pathogen Panel*
GT	*Georgia Institute of Technology*
INS	*Instituto Nacional de Saude (National Institute of Health, Mozambique)*
IRB	*Institutional Review Board*
LSHTM	*London School of Hygiene and Tropical Medicine*
MapSan	*Maputo Sanitation Trial*
MISAU	*Ministry of Health, Mozambique*
MPN	*Most Probable Number*
NCE	*No Cost Extension*
PMP	*Performance Monitoring Plan*
STH	*Soil-Transmitted Helminths*
TAG	*Technical Advisory Group*
UF	*University of Florida*
UNC	*University of North Carolina at Chapel Hill*
URC	*University Research Co., LLC*
US	*United States*
USAID	*United States Agency for International Development*
WASH	*Water, sanitation and hygiene*
WSUP	*Water and Sanitation for the Urban Poor*

Executive Summary

This is the final report describing the work undertaken by the MapSan Trial consortium and complements the two annual reports (2015 and 2016) already submitted. The MapSan consortium is led by the prime-awardee, the London School of Hygiene and Tropical Medicine (LSHTM), and includes the following partners, or sub-awardees: The Georgia Institute of Technology (GT), the Ministry of Health for Mozambique (MISAU), the University of North Carolina (UNC), the University of Florida (UF), and Water and Sanitation for the Urban Poor (WSUP). This report describes final progress against the project objectives and details all completed activities through to the end date (May 15, 2017).

Key activities were completed as specified by the grant in time for project close-down in April 2017. These included: completion of endline survey; preparation of scheduled papers and the completion of financial and administrative requirements.

Laboratory analysis of samples is ongoing and will be completed late 2017 with final analysis of data to be completed in early 2018.

Introduction

Access to safe sanitation in low-income, informal settlements of Sub-Saharan Africa has not significantly improved since 1990. The combination of a high faecal-related disease burden and inadequate infrastructure suggests that investment in expanding sanitation access in densely populated urban slums can yield important public health gains. No rigorous, controlled intervention studies have evaluated the health effects of decentralized (non-sewerage) sanitation in an informal urban setting, despite the role that such technologies will likely play in scaling up access. The MapSan trial is a controlled, before-and-after (CBA) trial to estimate the health impacts of an urban sanitation intervention in informal neighbourhoods of Maputo, Mozambique, including an assessment of whether exposures and health outcomes vary by localized population density.

The intervention consists of private pour-flush latrines (to septic tank) shared by multiple households in compounds or household clusters. MapSan has measured objective health outcomes in children drawn from the intervention, matched with controls using existing shared private latrines in poor sanitary conditions, at two time points: immediately before the intervention and at follow-up after 12 months. The primary outcome is combined prevalence of selected enteric infections among children under 5 years of age. Secondary outcome measures include soil-transmitted helminth (STH) reinfection in children following baseline deworming and prevalence of reported diarrheal disease. The study has used exposure assessment, faecal source tracking, and microbial transmission modelling to examine whether and how routes of exposure for diarrheagenic pathogens and STHs change.

The MapSan project activities for the duration of the project are described under three headings: (1) Project management and stakeholder engagement; (2) Research activities; and (3) Preliminary results and findings.

Project management and Stakeholder Engagement

Project management and stakeholder engagement activities have been successfully implemented and this report forms part of the closedown of the contract. Multiple no cost extensions (NCEs) were required as the initial duration of the contract was less that the stated period of time required to implement the study protocol. Requesting multiple NCEs for the prime and then issuing NCEs to sub-awardees was time consuming but the implementation of research activities was not delayed.

Ethical approval for the MapSan Trial was initially granted by the Ethics Committee of London School of Hygiene and Tropical Medicine (LSHTM) and the National Bio-Ethics Committee of Mozambique (CNBS) and the trial was registered on a public trial registry (www.clinicaltrials.gov) prior to study participant enrolment as per best practice. Following this, other academic partners (Georgia Institute of Technology (GT), *University of North Carolina at Chapel Hill (UNC) and University of Florida (UF));* secured ethical approval for their participation in the study from their respective Institutional Review Boards (IRB). All amendments to the study protocol received ethical approval from the LSHTM Ethics Committee and CNBS prior to implementation.

Following the inception of the MapSan Trial, the consortium has successfully raised additional funds from other donors to support related work which is complementary to the main trial. This includes a cohort study for the effect of sanitation on oral rotavirus vaccine immunogenicity funded by the Centres for Disease Control Foundation (CDCF) and funding from the Bill and Melinda Gates Foundation (BMGF) to: conduct a social-behavioural investigation of the intervention; perform a cost-effective analysis of the intervention; and to conduct a 24-month follow-up survey to assess the effect of the intervention on childhood nutritional outcomes.

As per the objectives of the URC TRAction programme, the MapSan team has engaged policy, practice and academic audiences throughout. The primary purpose of this engagement has been to gather inputs into the study design and delivery, generate interest in the project, and to create demand for research findings in advance of the study's completion. This approach is expected to increase the likelihood that the study findings will be used in policy and practice. These activities have been reported in the two MapSan Annual Reports submitted earlier and future planned activities post-closedown of the grant have been described in the Research Uptake Plan submitted in June 2017. In 2017 findings will be presented at the University of North Carolina's Water and Health Conference in Chapel Hill, USA, the Stockholm World Water Week in Stockholm, Sweden, the American Society of Tropical Medicine and Health Conference in Baltimore, USA, and the International Conference on Urban Health in Coimbra, Portugal.

RESEARCH ACTIVITIES

SUMMARY

A full account of research activities through December 2016 is provided in the previously submitted MapSan Annual Reports (2015 and 2016). Subsequent to the last annual report, the endline data collection has been successfully completed and samples are undergoing laboratory analysis at GT in Atlanta, USA. As per the stated final deliverables of the project, we submitted the following manuscripts to URC in June 2017:

1. Brown et al. *A controlled, before-and-after trial of an urban sanitation intervention to reduce enteric infections in children: research protocol for the Maputo Sanitation (MapSan) study, Mozambique*. Published 2015 in BMJ Open
2. Watson et al. *The association between shared sanitation and childhood diarrhoea, and stunting in low-income, informal urban settlements of Maputo, Mozambique: evidence from a cross-sectional study*. To be submitted to Tropical Medicine and International Health.
3. *Knee et al. A controlled, before-after trial of an urban sanitation intervention to reduce enteric infections in children: baseline results from the Maputo Sanitation (MapSan) study, Mozambique.* To be submitted to PLOS Medicine.

In addition, the following additional manuscripts are currently in development:

1. Rheingans et al. *Modelling the interactions between population density, sanitation coverage and socio-economic inequalities in low-income urban environments.* Expected submission: October 2017
2. Liang et al. *A quantitative framework for assessing the effects of sanitation on transmission of enteric pathogens among children under five in urban environment of Mozambique.* Expected submission: October 2017
3. Liang et al. Modelling transmission of soil-transmitted helminths (STHs) in Maputo, Mozambique – risk factors and the effects of sanitation improvement. Expected submission: November 2017
4. Holcomb et al. *Measuring the effect of a sanitation intervention on exposure to faecal contamination in the domestic environment in Maputo, Mozambique using traditional and host-specific faecal indicator*. Expected submission: December 2017

Beyond these manuscripts which are in active development, there will be a number of additional papers including the primary outcome results paper which we expect to submit for publication in March 2018.

Information on the completed endline survey is presented below along with information from the laboratory analysis completed to date.

DATA COLLECTION

Study enrolment began on February the 2nd 2015 and at the completion of baseline data collection; February 2016; 536 children from control compounds and 447 children from intervention compounds were enrolled (Figure 1). Following the initial baseline phase, 100 additional intervention latrines were constructed within the study area between November 2016 and May 2017. An additional 94 children were enrolled from the new intervention compounds, bringing the total number of intervention children enrolled to 541. The study area, from which both intervention and control clusters were drawn, spans over 16 bairros – or neighbourhoods - on the outskirts of downtown Maputo.

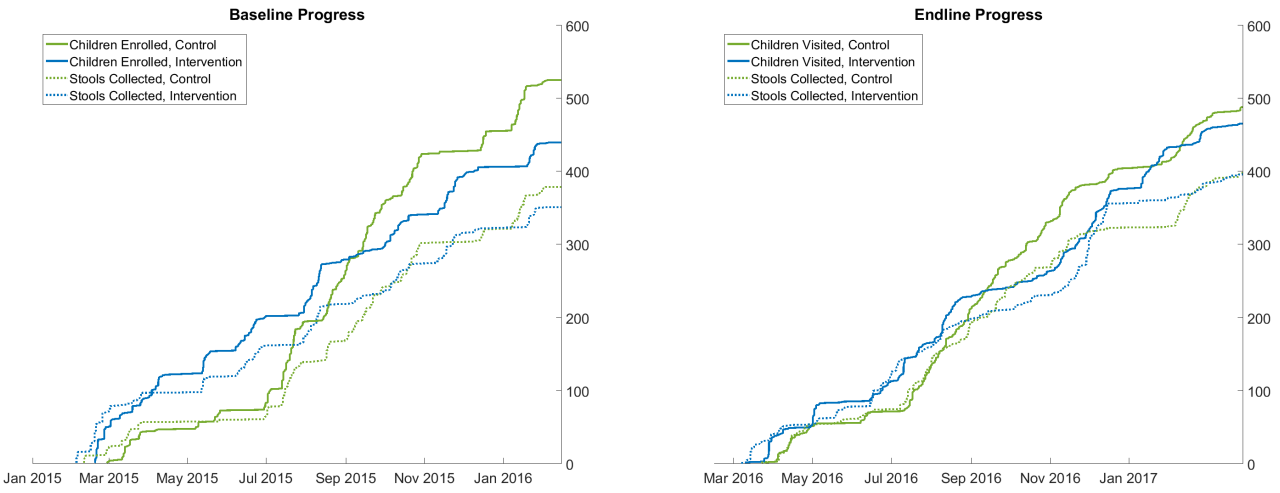

Figure 1: Cumulative enrolment/visitation of children and stools collected in intervention & control arms at baseline and endline

Endline data collection began after the completion of baseline data collection in February 2016. Enrolment in the study cohort was progressive: a total of 199 and 217 additional children were enrolled in the intervention and control arms, respectively, during endline. The amount of loss to follow-up was high in both arms: 144 intervention and 216 control children who were enrolled at baseline were unavailable at endline (Table 1). The main causes of loss to follow-up was population churn (i.e. children or households moved or were traveling for extended periods). There were 5 deaths and 8 caregivers refused to continue in the study.

Intervention compounds were visited 12 months after they began using their newly constructed latrine; an average of 50 days after baseline enrolment. The matched control compounds were visited 12+ months after baseline enrolment. Survey data, biometrics, and all samples (stool, saliva, water, soil, flies) were collected for all study sites as per protocols.

Table 1: endline visitation and sample collection completed

	Intervention n (% of available children, n=517)	Control n (% of available children, n=585)
Children eligible for endline visitation	661	8001
Children lost to follow-up (moved, died, traveling)	144	216
Children available for endline visitation (not lost to follow-up)	517 (100%)	585 (100%)
Child surveys completed for available children	424 (82%)	435 (74%)
Stools collected	423 (81%)	430 (74%)
Children with completed survey and stool collected	356 (69%)	351 (60%)

During endline data collection, stools were collected from 81% and surveys from 82% of the 517 available intervention children (Table 1). Stool samples and survey data were collected from 74% of the 585 children available in the control group (Table 1). The rate of endline visitation, data and stool collection, was similar to the rate of enrolment at baseline (Figure 1, Figure 2).

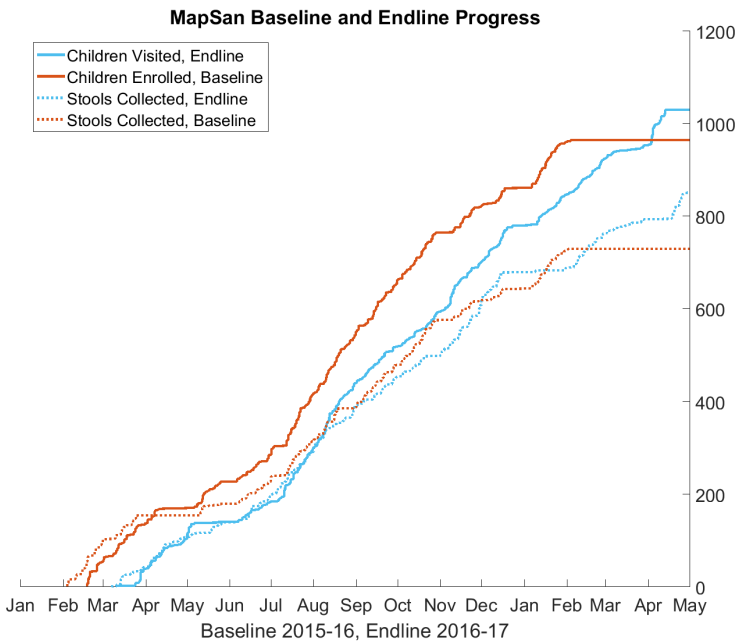

Figure 2: Cumulative enrolment/survey completion and stool collection for baseline & endline

DEWORMING

All compounds enrolled in the MapSan trial were provided with 400-mg of Albendazole for deworming. For intervention compounds, deworming was conducted once the compound began to use their newly constructed WSUP latrine. On average deworming occurred within 17 days of the latrine first being used. For control compounds deworming occurred following baseline enrolment. On average there were 28 days between enrolment and deworming of control compounds. A second round of deworming was completed just prior to the completion of endline visitation (January – March 2017).

STOOL AND SALIVA SAMPLES

Enumerators attempted to collect stool samples from every child enrolled in the study at each time point. During the baseline phase a total of 396 and 410 stool samples were collected from children in the intervention and control arms, respectively (Figure 1, Figure 2). A total of 764 saliva samples were collected from 366 intervention children and 398 control children at baseline. During the endline phase, stool samples were collected from 423 and 430 children in the intervention group and control group respectively (Figure 1, Figure 2), and saliva samples were collected from 398 intervention and 439 control children. All stool samples were transported to MISAU for immediate analysis by Kato-Katz and storage. Four sub-samples of each stool were stored at -80°C until future analysis or shipment to GT. Saliva samples were transported to MISAU on the day of collection and immediately stored at -80°C.

Using the Kato-Katz technique stool samples were examined by the MISAU laboratory under 10 – 40x magnification to identify the presence of STH ova. Laboratory technicians counted the number of hookworm, *Trichuris trichiura*, fertile and in-fertile *Ascaris lumbricoides* eggs, and *Enterobius vermicularis* present in the slide preparation. Counts were transformed into concentrations of ova/g by multiplying by a factor of 24. In addition to enumerating the above species ova, technicians determined whether the following STH species are present in the sample preparation: *Taenia species, Hymenolepis nana* and *Hymenolepis dimunita*.

During this reporting period, all baseline stool samples were received by GT for analysis of the primary outcome: combined non-viral, non-STH enteric infection; using the Gastrointestinal Pathogen Panel (GPP) multiplex molecular assay. To date, 715 baseline stools samples have been analysed by the GPP. All stool samples have now been received by GT and to date just over 65% of the endline samples have been analysed by GPP.

RESULTS

Baseline data collection, including the expanded baseline sample, was completed in early 2017. Below is a preliminary descriptive analysis of baseline data including demographic information, health status data and information about environmental conditions.

BASELINE ENVIRONMENTAL CHARACTERISTICS

A series of key characteristics of intervention and control compounds at baseline are detailed in Table 2. This data, along with the health status data, has been used to assess the comparability between the two trial arms, ensuring any significant differences can be accounted for in the final analysis. The difference in access to a water tap in compounds and the mean number of people residing in compounds in the intervention arm and control arm will be accounted for. It should be stressed that these numbers are not final and a formal analysis of baseline data is planned for the third quarter of 2017.

Table 2: Baseline characteristics of enrolled intervention & control compounds

	Intervention	Control	Total
Total sites (compounds) enrolled	275 (233 SL, 42 CSB)	299	574
Mean # people/compound*	17.2	14.1	15.6
Mean # children/compound	2.1	1.9	2.0
Water tap in compound*	85%	74%	79%
Animals present in compound	61%	61%	61%
Flooding during rainy season	59%	65%	62%
Latrine characteristics			
Drop hole cover present	59%	55%	57%
Pedestal/masonry present	40%	38%	39%
Superstructure present	30%	25%	28%

*Significantly different at p = 0.05 (unadjusted)

BASELINE CHARACTERISTICS OF ENROLLED CHILDREN

Table 3 below shows the age distribution and characteristics of children enrolled in intervention and control arms. Characteristics of children enrolled in both arms are well balanced. The difference in the proportion of females enrolled in intervention and controls arms will be accounted for in the final analysis.

Table 3: Characteristics of enrolled children at baseline

	Intervention	Control	Total
# children enrolled	541	536	1077
Age groups			
0-11 months	28%	28%	28%
12-23 months	27%	27%	27%
24-48 months	43%	42%	43%
Female*	44%	52%	48%
Breastfed, exclusively	10%	9.0%	10%
Child defecation			
Diapers	63%	65%	65%
Latrine	9.1%	11%	10%
Other (open defecation, bucket)	27%	23%	25%

*Significantly different at p = 0.05 (unadjusted)

POPULATION DENSITY

One objective of the MapSan study is to assess whether population density modifies the effect of the sanitation intervention on child health outcomes. Population density is being assessed in two ways: (1) by measuring compound area and calculating the number of people per square meter of living space; and (2) by using satellite imagery and a rooftop area algorithm to calculate the number of people living within 50 meters and 100 meters of study compounds. Figure 4 illustrates density method (2), depicting a section of the satellite imagery overlaid with rooftop delineations within a 50-meter radius.

Figure 3: Satellite imagery of the study area (left) with rooftop delineations within a 50-meter radius (right).

BASELINE DISEASE BURDEN

Baseline primary outcome data by study arm:

Primary outcome data are derived from molecular analysis of stool specimens by the GPP assay at GT and are presented in Figure 4. Overall, the combined prevalence of non-STH, non-viral enteric infections was 84% in the intervention arm and 88% in the control arm at baseline, which was not significantly different. Because our sample size calculations assumed an overall prevalence of 71% at baseline, this higher prevalence results in greater statistical power for trial data analysis. The most frequently detected enteropathogens, irrespective of study arm were *Giardia* (52%), *Shigella* (45%), ETEC (31%), and *Salmonella* spp. (21%).

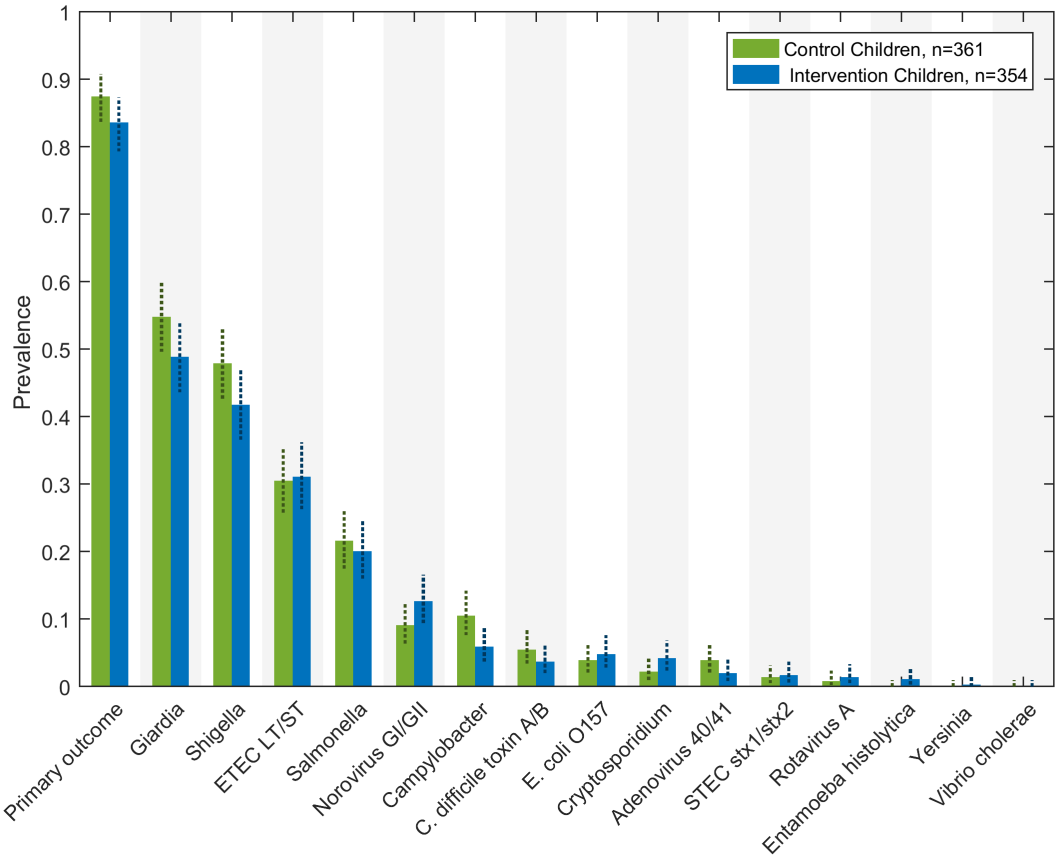

Figure 4: Baseline prevalence of enteric pathogens in stool samples of intervention & control children

Baseline primary outcome results by age:

The prevalence of the primary outcome and the two most frequently detected entereopathogens, *Giardia* and *Shigella*, increased with child age. The prevalence of most other individual enteric pathogens was similar across age groups with the exception of norovirus GI/GII and *Salmonella*, which decreased with increasing age. In general, the prevalence of infection with one or more bacterial or protozoan pathogen increased with increasing age and the prevalence of enteric viral infection decreased with increasing age. Enteric pathogen coinfection also increased with age. Figures 5, 6, and 7, present prevalence data by *a priori* age strata.

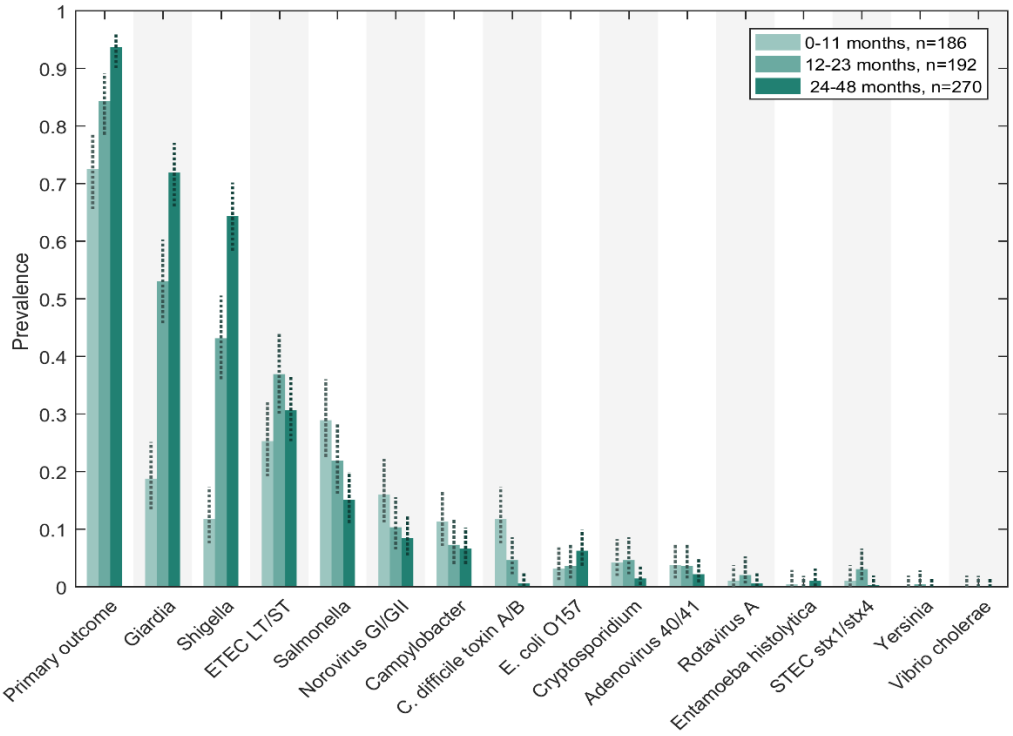

Figure 5: Baseline prevalence, by age group, of enteric pathogens detected in stool by GPP assay.

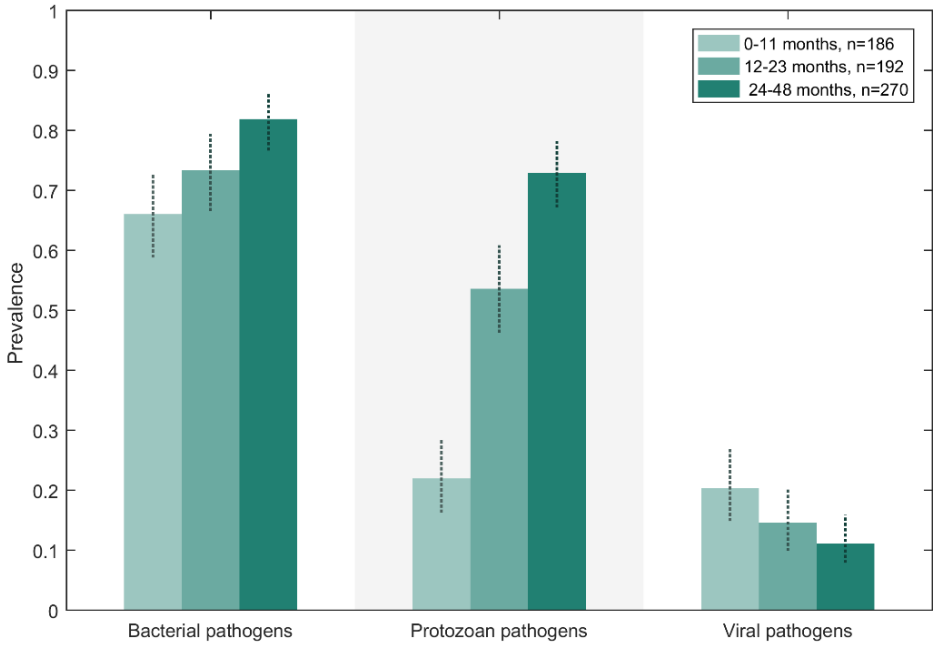

Figure 6: Baseline prevalence of 3 classes of enteric pathogen by age group.

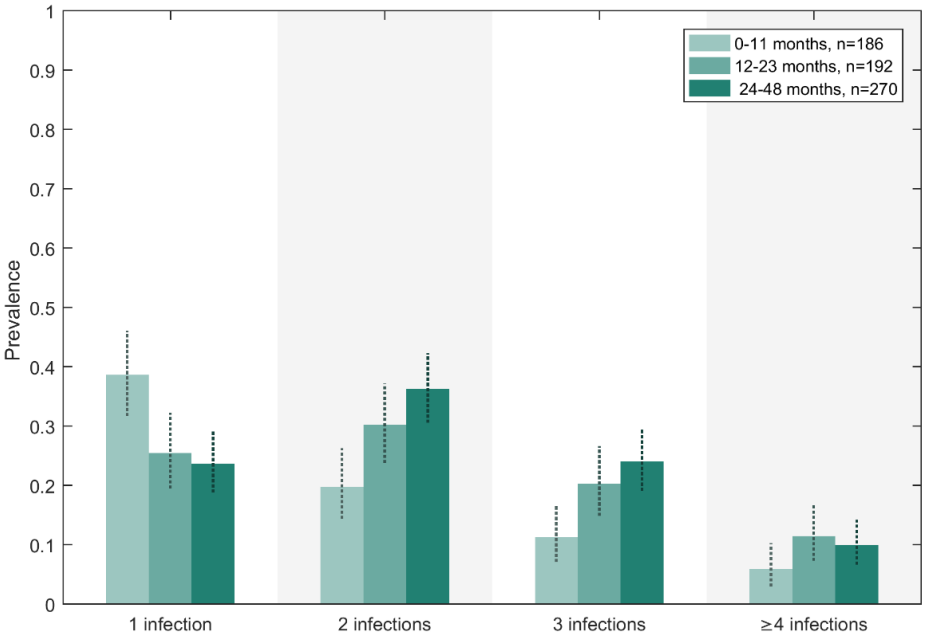

Figure 7: Baseline prevalence of enteric pathogen co-infection by age group.

The two secondary outcomes of the MapSan study are: STH reinfection following baseline deworming; and reported incidence of diarrhoea among enrolled children. Figure 8 below shows the age distribution of caregiver-reported diarrhoea among enrolled children from intervention and control groups at baseline. At baseline the incidence of caregiver-reported diarrhoea is highest in children aged between 1 – 24 months.

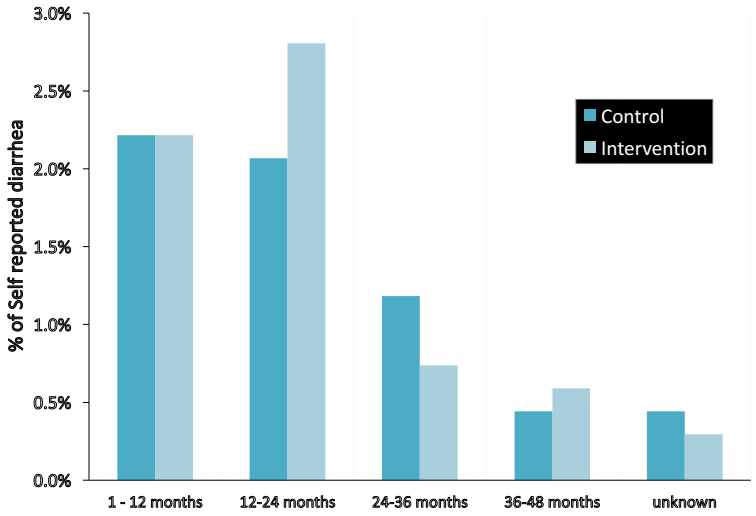

Figure 8: Age distribution of (caregiver-reported) diarrhoea among enrolled children from intervention and groups at baseline control

Baseline STH data

All baseline stool samples (n=745) were analysed for the presence of STH ova using the Kato-Katz technique at the MISAU laboratory in Maputo. Overall baseline prevalence for any STH infection by Kato-Katz was 44% and is similar between study arms (Figure 9). As expected, prevalence increases with age (Figure 9). *T. trichuris* and *A. lumbricoides* are the most commonly observed STHs with prevalence rates of 37% and 23%, respectively. Coinfection with multiple STH was observed in 16% of samples (Figure 10) and increased with age. An initial assessment of balance between intervention and control arms of the trial showed no statistically meaningful difference in STH prevalence. Covariates related to sanitation conditions (e.g., presence of a pedestal or drop-hole cover) or to household conditions and demographics (e.g., presence of any floor covering, number of people living in the household, education level of the primary caretaker, socio-economic status) were not significant risk factors for STH infections.

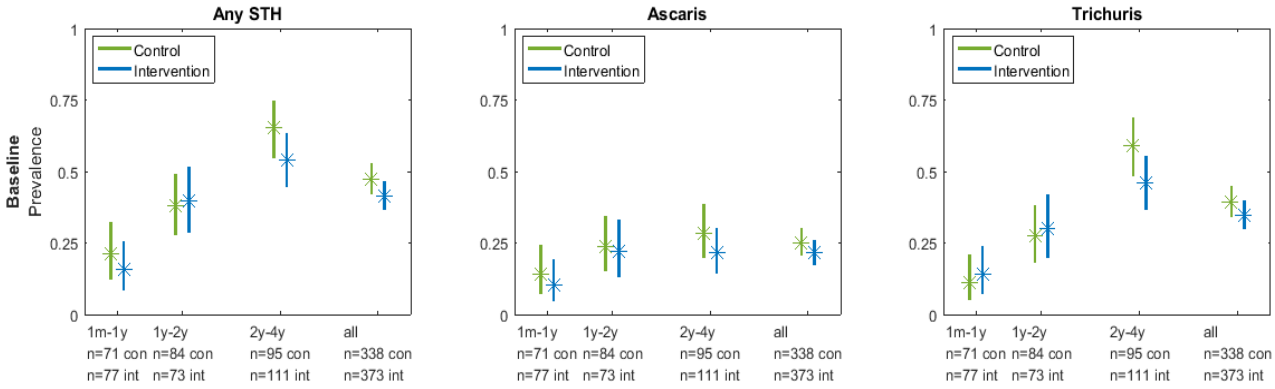

Figure 9: Baseline prevalence of any STH infection, Ascaris, and Trichuris.

Stratified by study arm and age group. Intervention mean and 95% confidence interval represented by blue markers and bars. Control mean and 95% confidence interval represented by green markers and bars.

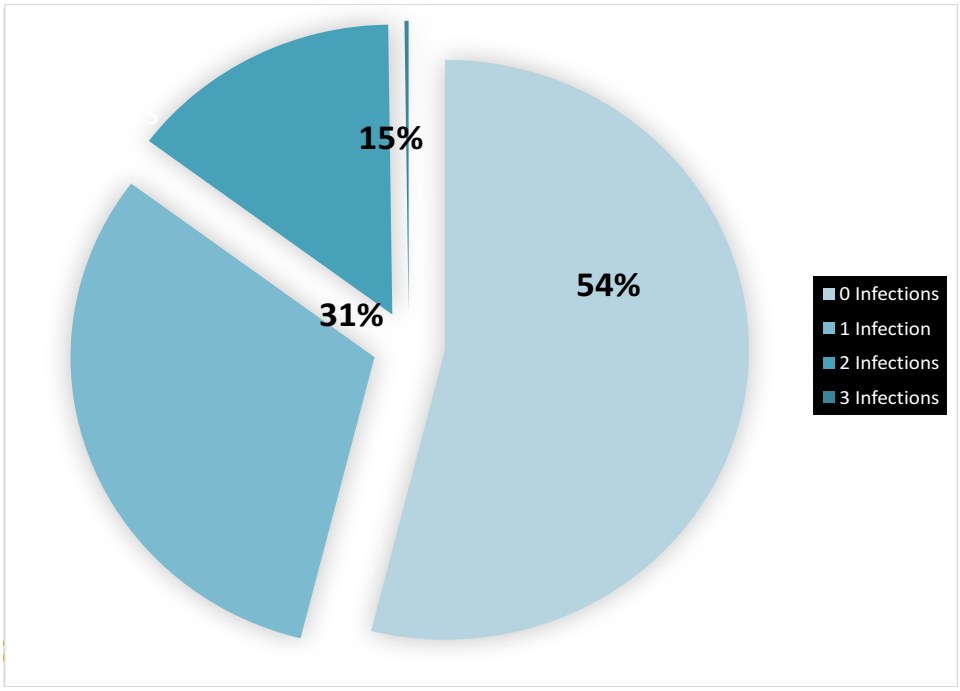

Figure 10: STH co-infections in children at baseline.

ENDLINE HEALTH STATUS

To date, 547 of the 853 samples collected at endline have been analysed using the GPP. Preliminary analyses of the endline GPP data show an overall primary outcome prevalence of 87% and 90% in intervention and control arms respectively. Similar to results at baseline, *Giardia*, *Shigella*, ETEC, and *Salmonella* were the most frequently detected pathogens among intervention and control children. Formal analyses of these data have not yet been performed and will be completed following the formal baseline analysis. Given that the laboratory analysis of endline samples has not been completed and the formal analysis of this data has not been performed; no inference should be drawn as to the effect of the intervention and any data presented here must not be shared externally nor published as this would be in contravention of the protocol and the conditions of the ethical approval for the study. The prevalence of coinfection remained high in the preliminary analysis: 68% of intervention children and 65% of control children were infected with two or more enteropathogens (Figure 12).

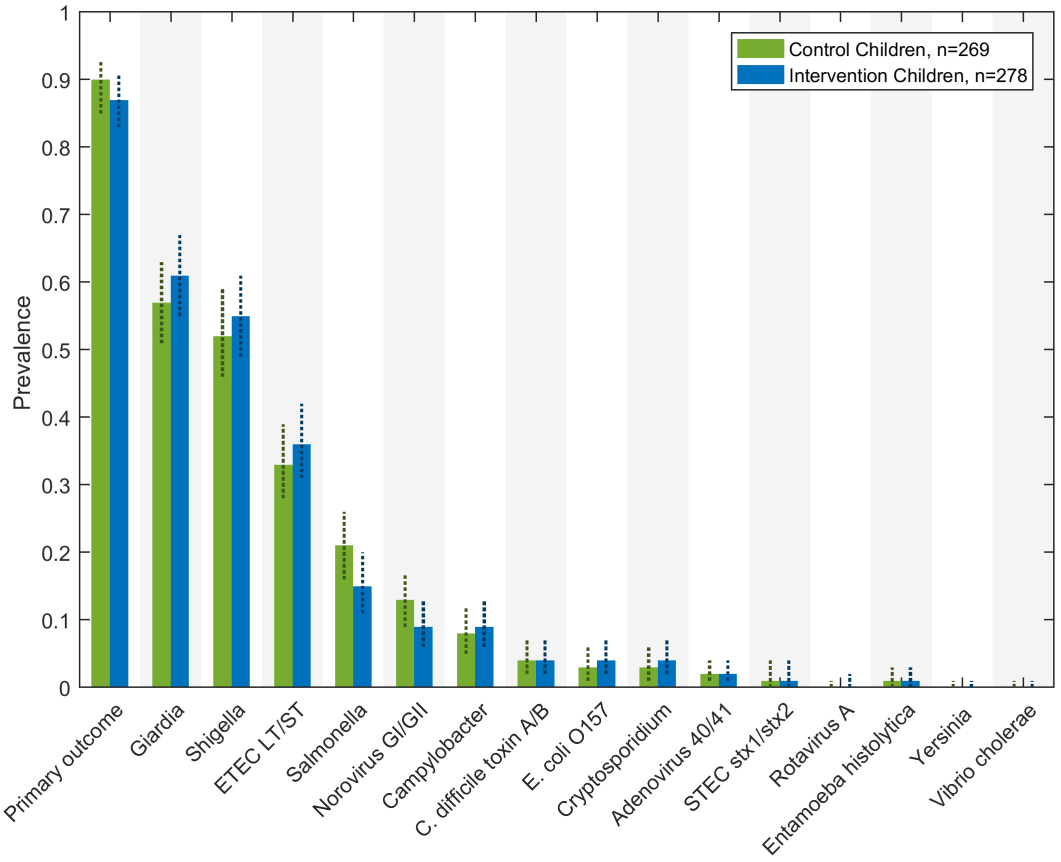

Figure 11: Endline prevalence of enteric pathogens by study arm.

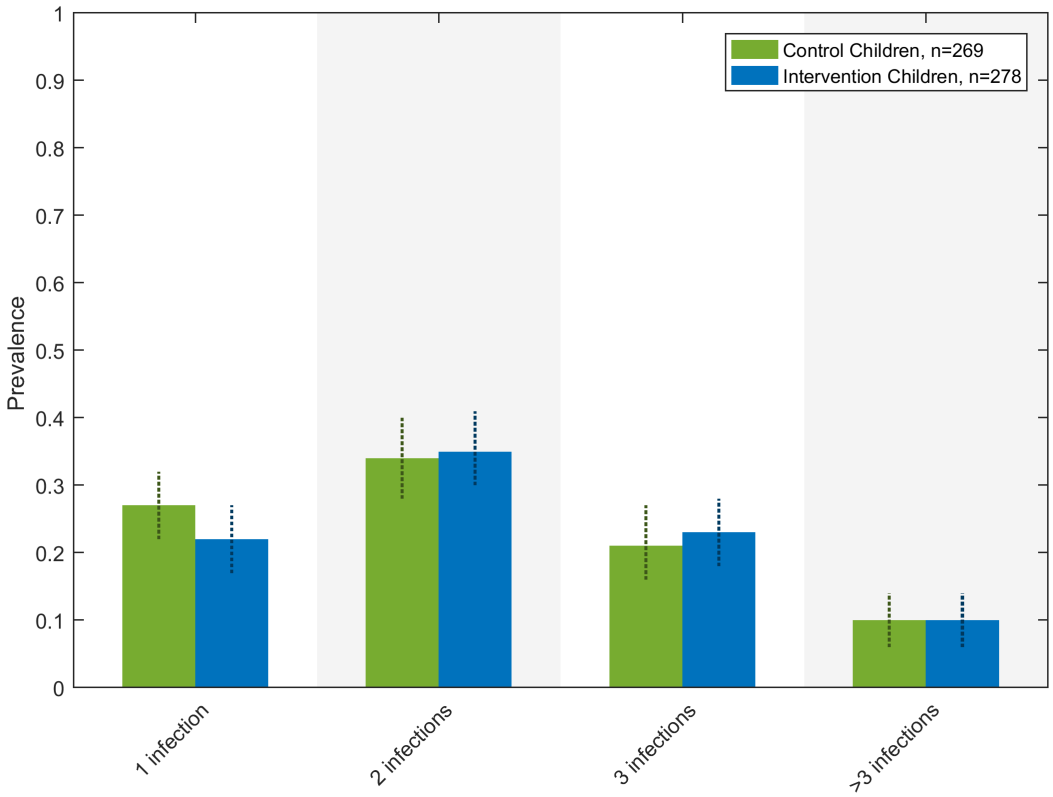

Figure 12: Endline prevalence of coinfection by study arm.

Similar to the findings at baseline, initial analysis of endline data suggests the most common STH infections in both the intervention and control children remain *T.Trichiura* and *A. lumbricoides* (Figure 13).

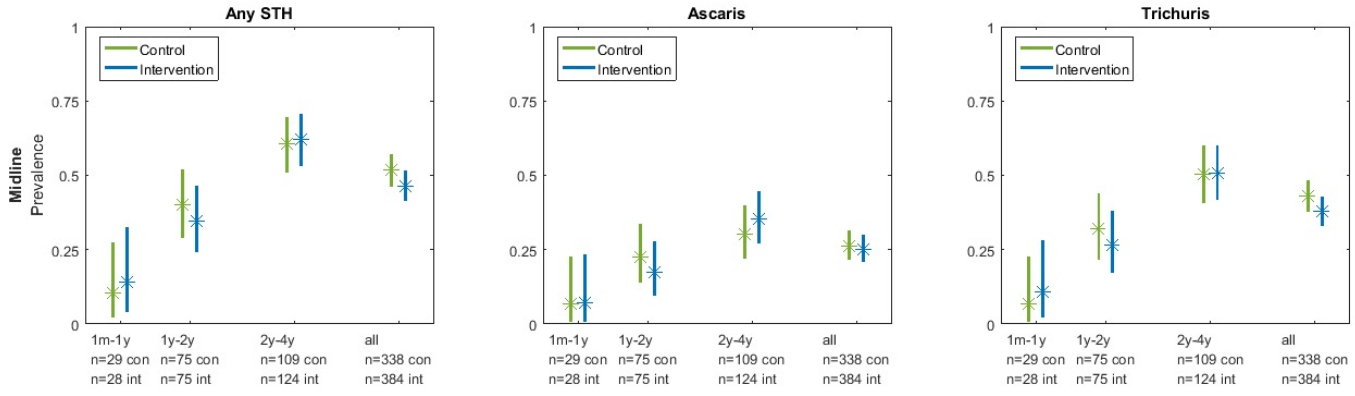

Figure 13: Endline prevalence of any STH, Ascaris, and Trichuris, by age, in intervention and control children.

Barriers and Challenges

Most challenges faced during the study were manageable and were addressed as they arose. However, the study encountered two significant challenges which whilst managed effected the execution of study activities:

Delays in construction and latrine handover in intervention sites:

Construction delays at the beginning of the project limited the number of compounds enumerators were able to visit and made field work less efficient overall. These delays resulted in slower than projected recruitment in the first months of enrolment as the rate of recruitment was dictated by the rate of construction. However, over time there were significant improvements in the rate of construction, with the last quarter of enrolment proceeding much faster. Uncertainties are inherent in latrine construction and handover to the community, and it was necessary to manage the pace of the field work to reflect this.

Uncertainty with regard to the No Cost Extension (NCE):

The study protocol specified a 12-month follow up period; however as the prime contract was signed in October 2014, backdated to August 2014 and ended in April 2016, it did not allow enough time for follow up. It was agreed with URC at that time that a NCE would be granted as a matter of course in early 2015 so that study could be implemented as per the approved protocol, but the NCE was not actually granted until late October 2015. As a result all the sub-contracts with sub-awardees had to be negotiated again and budgets and workplans had to be adjusted accordingly. This placed pressure on administrative and financial resources, and created a high burden of expenditure and task completion required in the final quarter of the project (January – March 2017). The three key areas of work during this period were: completion of the endline survey as per the timeline and ensuring a high return rate of stool samples from children that provided samples at baseline; finalisation of data analysis for the preparation of the scheduled papers; completion of financial and administrative aspects of the grant, including issuance of NCE to sub-awardees. In addition, closing the grant before completion of pre-specified and pre-planned study activities (i.e. the laboratory analysis of samples, statistical analysis of the final datasets, and the preparation of key manuscripts) presented challenges for the study team in ensuring that these activities could be completed after the project closedown.

Conclusions and Recommendations

This study has successfully engaged policy, practice and academic audiences throughout the duration of the study period. This is evidenced by the high number of manuscripts developed for publication and presentations given at key public health and WASH conferences; and by successfully attracting additional funding streams to complement and further the research objectives.

Key activities were completed as specified by the grant in time for project close-down in April 2017. These included: completion of endline survey; preparation of scheduled papers and the completion of financial and administrative requirements.

Preliminary analysis of baseline characteristics for intervention and control compounds suggested that the study's matching strategy yielded reasonable balance, although this will be analysed further over the next few months. Baseline disease burden was even higher than estimated; demonstrating the critical need for an evidence-based intervention. Formal analysis of endline health status remains to be conducted; however, preliminary analysis suggests prevalence of coinfection and STH infection remained high in both intervention and control arm. No inference should be drawn as to the effect of the intervention until formal analysis is undertaken.

Next steps

Formal analysis of baseline and endline characteristics will be completed in late 2017. Additional research will investigate the social-behavioural impact of the intervention, and a planned follow-up survey at 24-months post intervention is planned to assess impact on child nutritional outcomes.