PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between vaccine preventable diseases in children and improved sanitation following a nationwide sanitation campaign in India- An ecological analysis
AUTHORS	Singh, Parvati; Forthal, Donald; Shah, Manisha; Bruckner, Tim-Allen

VERSION 1 – REVIEW

REVIEWER	Barutcu, Adnan Çukurova Üniversitesi Tıp Fakültesi, Department of Pediatrics
REVIEW RETURNED	10-Nov-2021

GENERAL COMMENTS	First of all, I would like to congratulate all the authors for this valuable work. It is seen that a great job has been accomplished with this enormous project in India on the sanitation of environmental factors and the construction of toilets for homes. In the study, it was planned to investigate the relationship between poor hygiene conditions and vaccine preventable diseases. However, it is planned to study with vaccine preventable diseases: diphtheria, tetanus, pertussis and measles. The transmission routes of diseases such as pertussis, measles, diphtheria are often airborne. Although vitamin A deficiency is a risk factor for measles; There is no evidence that malnutrition and/or undernutrition is an aggravating or predisposing factor for these diseases. Researchers may have wanted to investigate whether there was an indirect effect. It is known that diseases that increase due to insufficient hygiene and sanitation, inadequate sewage system, inability to clean drinking water, non-compliance with hygiene rules such as hand washing and various impossibilities are mostly diseases transmitted by fecal-oral route. In such a dataset, researching diseases such as poliomyelitis, cholera, salmonella, hepatitis A and rotavirus could yield much more striking results. In the abstract; The introduction should be rearranged in accordance with the title. The results section could be a little more detailed. The introduction section is too long and at some points the integrity of the subject is broken. In the discussion part; The sentences previously mentioned in the results section are repeated unnecessarily. It is recommended that the title of limitations of the study should be placed just above the conclusion paragraph. In addition, there is a rotavirus paragraph independent of the subject described and discussed in the

	paragraphs after the limiting features of the study. It is recommended that these parts be removed and rearranged. Although it was mentioned within the limitations of the study, the presence of a table summarizing the sociodemographic characteristics of the children included in the study could have brought the study to a better level.

REVIEWER	Theeten, Heidi Universiteit Antwerpen
REVIEW RETURNED	19-Nov-2021

GENERAL COMMENTS	The subject is interesting in its attempt to disentangle the effect of vaccination and sanitory intervention to reduce infectious disease burden in infants. The manuscript could be improved however, mainly by extending beyond the main hypothesis which is too narrow, and also by considering some more confounder variables. Introduction 1. The introduction mainly focuses on the role of the sanitation program in preventing ileo-jejunitis and associated immune responses. Another quite evident mechanism is direct infection at shared toilets, which is a possible transmission pathway for measles that is also reduced by the program. This mechanism is not highlighted introduction nor in the discussion. 2. Line 18: You say "India's abysmal global ranking raises questions about low vaccine effectiveness despite its over 90% immunization coverage following the initiation of the Universal Immunization Program in 2012" – this sentence implies that vaccination coverage is already optimal while in your table 1 it shows vaccination rates of 78-80% for under 1 year old children? This might be rephrased. 3. Small correction: line 51: change "SBM aims" to "SBM aimed", their aim was to have this done by 2019 which has passed already. Methods - On p8 line32 is stated that ratio is reconverted to prevalence using the number of children reporting any disease. What about children that report no disease? Also, nutrition status is not among the confounders corrected for, which is a pity as it is a strong predictor of immune response. Is no information available on nutrition status of children in India? If this is the case, this limitation should be discussed with its implications. Results: - Page 12, line 40: When speaking about toilet availability you say that "The most visible improvements occur in Rajasthan"; but above on line 25 you said that no substantial decline in prevalence of measles was shown in this district. Although you found an overall decline in measles cases over a period when toilet availability increased, the narrative of this study could be toned down a bit. Factors such as degree of urbanization e.g. were not checked for. Discussion - Page 13, line 42: you state that "Findings provide proof-of-concept that improvements in ambient sanitation may augment universal immunization efforts in reducing the burden of measles among u5 children in India". This is put a bit too strongly. I suggest

	to delete proof-of-concept and rephrase this sentence as additional studies are required to really point to an association between the two findings. - Page 13, line 54: given this study is still observational, I would suggest to delete the phrase "which lends a quasi-experimental design to our analysis" - measles prevalence decrease on its own is expected to have an impact on other (vaccine preventable) infections, as measles induces immune depression. Has this effect been taken into account? Please discuss on this issue as well. Conclusion - Should be rephrased and toned down. From the results it is clear that there is only a small reduction in measles cases (decrease of 1.12 measles cases for a 7% increase in household with toilets) Appendix Table A.3: - It says "%age" in the table, this seems incorrect

REVIEWER	Verdonck, Kristien Institute of Tropical Medicine
REVIEW RETURNED	29-Dec-2021

GENERAL COMMENTS	This manuscript addresses an interesting topic, uses relevant data, and is written clearly and transparently. Nevertheless, as explained below, I have some concerns about the authors' claim that the study provides proof-of-concept that improvements in sanitation augment immunization efforts in reducing the burden of measles in India. Major comments - A before-after comparison as only argument is not sufficient to claim 'proof of concept' (in my opinion). What if the incidence of measles is steadily decreasing over the years? What if there was a measles outbreak in 2013? If that were the case, the incidence would decrease after 2013 regardless of the intervention. Although the authors did adjust their analysis for potentially confounding factors, I am not convinced that all relevant confounding is captured. The addition of other arguments could make the case more convincing, for example spatial arguments (districts with good sanitation have less vaccine-preventable diseases than districts with poor sanitation at any point in time). The addition of intermediary factors (such as toilet use, malnutrition, environmental enteropathy) could also help. - Only two time points (2013 and 2016) are included in the evaluation. What about yearly variation in the frequency of vaccine-preventable diseases? Considerations of variability over the years are relevant (and I understand from the methods' section that this information is available?). In the case of measles, as the authors recognise: "the highly contagious nature of measles (relative to diphtheria, pertussis and tetanus) may impart greater amenability to change, following SBM." But the amenability to change is also possible regardless of SBM? - I believe that there are more limitations. Example 1: is there any indication (in the present study) of toilet use and of improvement of nutritional status due to the intervention? As the authors do not present data about such intermediary steps, we can only speculate on how exposure and outcome are linked. Example 2: the data about the exposure before and after the intervention comes from different sources. How could this affect the findings?

	- The authors mention the quasi-random nature of the SBM programme. What is meant exactly and how does this affect the authors' before-after comparison? How is this a strength of the study? - The authors do not discuss two issues that may affect the findings. (1) Spatial considerations/dependency (do districts that are near resemble each other more than districts that are far away?) and (2) Statistical instability (is the number of cases small in some (small) districts so that small changes in the number of cases (a few cases more or less) have a large effect on the prevalence/incidence?). - P12, first paragraph and appendix table A.1. Why was this approach used and what is the main message? Does it mean that the largest changes in outcome were seen in the (few) districts with the most extreme exposure levels? Is it possible that this table reflects statistical instability? - What was the effect of the inclusion of candidate confounders on the coefficient (beta1)? Which variables had the largest effect? - Could Vitamin A supplementation (which increased during the study period) be a confounding factor? Minor comments - The paragraph on ‘what is already known’ suggests that the study will estimate the strength of the association between open defecation, child malnutrition and vaccine efficacy. The study does not really fill this gap, as it only looks at self-reported availability of toilets and publicly reported (notified) cases of four vaccine-preventable diseases. - Abstract and introduction. “India consistently reports the most diphtheria, pertussis, tetanus and measles cases worldwide.” This is not surprising given the large population size of India. I consider that the incidence per 100,000 (or per 1000) inhabitants per year would be a more interesting measure of disease frequency. - Introduction. ‘High burden of child mortality from VPDs’. How high is this burden? Any references for incidence of infections and deaths per population? - The outcome of interest is the change in prevalence of four vaccine-preventable diseases at district level. I consider that in this context, “annual incidence” is a more appropriate description of disease frequency than “prevalence”. - Does the environmental enteropathy occur at the age at which infants/children are vaccinated for the four vaccine-preventable diseases? Any references supporting this? - P7 ‘thus far’: It is unclear to the reader when this was written. - P11. Why did the authors expect that errors would be correlated? - Table 1. The authors present the difference of two means (before-after). The mean of the differences (for all the districts) may be more appropriate here? - Figure 1 and 2. A two-colour scale would be clearer (one colour for increase and another colour for decrease). - Equation 1. Regarding the term with beta2. I wonder if the authors considered using a mixed model. Is this term with beta2 used as an equivalent of a random effect per district? I wondered if there is any advantage of the approach in equation 1 over a mixed model with a random effect? - I was surprised to find that none of the authors has an affiliation with an institute in India.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Adnan Barutcu, Çukurova Üniversitesi Tıp Fakültesi
Comments to the Author:
First of all, I would like to congratulate all the authors for this valuable work.
It is seen that a great job has been accomplished with this enormous project in India on the sanitation of environmental factors and the construction of toilets for homes.

Response: We thank the Reviewer for his endorsement.

In the study, it was planned to investigate the relationship between poor hygiene conditions and vaccine preventable diseases. However, it is planned to study with vaccine preventable diseases: diphtheria, tetanus, pertussis and measles.
The transmission routes of diseases such as pertussis, measles, diphtheria are often airborne. Although vitamin A deficiency is a risk factor for measles; There is no evidence that malnutrition and/or undernutrition is an aggravating or predisposing factor for these diseases. Researchers may have wanted to investigate whether there was an indirect effect. It is known that diseases that increase due to insufficient hygiene and sanitation, inadequate sewage system, inability to clean drinking water, non-compliance with hygiene rules such as hand washing and various impossibilities are mostly diseases transmitted by fecal-oral route. In such a dataset, researching diseases such as poliomyelitis, cholera, salmonella, hepatitis A and rotavirus could yield much more striking results.

Response: We agree with the Reviewer that examination of polio, cholera, salmonella, hepatitis A and rotavirus would be well-suited to our exposure of interest. However, polio was eradicated in India in March 2014, before the initiation of the national sanitation campaign (SBM). Hence, we did not examine polio. With respect to the other diseases mentioned, unfortunately, the HMIS datasets do not provide information on these diseases or outbreaks. Furthermore, we do not know of any comprehensive, nationally representative, publicly available datasets that report on surveillance of these diseases among under 5 years old children. We now note this point in the Discussion and encourage future research to examine these outcomes once the appropriate data become available.

We also appreciate the Reviewer's suggestion to investigate whether undernutrition serves as an "indirect effect" of the relation between SBM and measles. Per this request, we now include, as a supplementary analysis, estimation of mediation of undernutrition among under 5 year old children. Through mediation analysis using structural equation modelling (Sobel, 1987; StataCorp, 2021), we may estimate both direct and indirect effects. We find that change in stunting among under 5 year old children (i.e., the measure of child undernutrition in our data) serves as a partial mediator of the relation between change in toilet availability and change in measles in this population. These results appear in Appendix Table A.5 and are also presented below:

Table R.1: Relation between change in percentage of households with toilets, change in stunting among under 5 years old children and their effect on change in measles among under 5 years old children estimated using structural equation modelling (N = 532).

Structural Equation Modelling Step 1: ***Direct effect*** of change in percentage of households with toilets on change in percentage of u5 children who are stunted.

Outcome = Change in percentage of u5 children who are stunted	Coefficient	95% Confidence intervals	
Change in percentage of households with toilets	-0.053*	-0.104	-0.002
Change in percentage of households with electricity	-0.114	-0.484	0.256
Change in percentage of households with clean drinking water	-0.081*	-0.161	-0.001
Change in percentage of households with clean cooking fuel	0.014	-0.062	0.089
Change in percentage of women with 10th grade or higher education	-0.214**	-0.329	-0.100
Change in percentage of ≤ 1 year old children with measles vaccination	-0.035	-0.091	0.021
Change in percentage of births in hospitals	0.042	-0.036	0.120
Change in percentage of u5 children who received Vitamin A supplementation	-0.028	-0.069	0.012
Structural Equation Modelling Step 2: ***Direct effect*** of change in percentage of households with toilets and change in percentage of u5 children who are stunted on change in measles among u5 children			
Outcome = Change in measles among u5 children	Coefficient	95% Confidence intervals	
Change in percentage of u5 children who are stunted	0.012*	0.023	0.002
Change in percentage of households with toilets	-0.320*	-0.617	-0.044
Change in percentage of households with electricity	0.147	0.008	0.286
Change in percentage of households with clean drinking water	-0.211	0.537	0.115
Change in percentage of households with clean cooking fuel	-0.168	0.477	0.140
Change in percentage of women with 10th grade or higher education	0.502	0.033	0.970
Change in percentage of ≤ 1 year old children with measles vaccination	-0.073	0.302	0.155
Change in percentage of births in hospitals	0.239	0.081	0.558
Change in percentage of u5 children who received Vitamin A supplementation	-0.203	-0.368	-0.038
Baseline (pre-SBM) Measles per 1000 u5 children	-0.772***	0.842	-0.701
Structural Equation Modelling Step 3: ***Indirect effect*** of change in percentage of households on change in measles among u5 children that passes through change in stunting among u5 children			

Outcome = Change in measles among u5 children	Coefficient	95% Confidence intervals	
Change in percentage of households with toilets	-0.042	-0.081	-0.004
Change in percentage of households with electricity	-0.023	-0.065	0.019
Change in percentage of households with clean drinking water	0.023	-0.020	0.065
Change in percentage of households with clean cooking fuel	0.008	-0.009	0.025
Change in percentage of women with 10th grade or higher education	0.002	-0.013	0.016
Change in percentage of ≤ 1 year old children with measles vaccination	0.004	-0.006	0.015
Change in percentage of births in hospitals	0.005	-0.008	0.019
Change in percentage of u5 children who received Vitamin A supplementation	-0.004	-0.012	0.005
Baseline (pre-SBM) Measles per 1000 u5 children	(no path)	(no path)	(no path)
Structural Equation Modelling Step 4: ***Total effect*** of change in percentage of households on change in measles among u5 children (if there is no mediator in our model)			
Outcome = Change in measles among u5 children	Coefficient	95% Confidence intervals	
Change in percentage of u5 children who are stunted	0.012*	0.023	0.002
Change in percentage of households with toilets	-0.362*	-0.617	-0.044
Change in percentage of households with electricity	0.124	-0.024	0.271
Change in percentage of households with clean drinking water	-0.188	-0.513	0.136
Change in percentage of households with clean cooking fuel	-0.161	-0.468	0.147
Change in percentage of women with 10th grade or higher education	-0.503	-0.168	0.161
Change in percentage of ≤ 1 year old children with measles vaccination	-0.069	-0.298	0.159
Change in percentage of births in hospitals	0.244	-0.075	0.563
Change in percentage of u5 children who received Vitamin A supplementation	-0.207	-0.372	-0.041
Baseline (pre-SBM) Measles per 1000 u5 children	-0.727***	-0.842	-0.701

**p<0.05, **p<0.01, ***p<0.001*

Step 4 in Table R.1 shows that the total effect coefficient of change in percentage of households with toilets on change in measles among u5 children is -0.362. This is the effect or association we would observe if there was no mediator in our analytic model. The direct effect coefficient of change in percentage of households with toilets on change in measles among u5 children is -.320, which is smaller than the total effect coefficient (Step 2). The indirect effect of change in percentage of households with toilets on change in measles among u5 children that passes through change in percentage of u5 children who are stunted is -0.042 (Step 3), indicating that stunting may only serve as a partial mediator in this analysis.

We can also interpret results from our structural equation modelling as ratios:

Proportion of total effect mediated = -0.042/-0.362 = 0.116 or about 12%. Put simply, about 12% of the total effect of change in percentage of households with toilets on change in measles among u5 children appears to be mediated by change in stunting among u5 children over our study period.

References cited:

Sobel, M. E. (1987). Direct and indirect effects in linear structural equation models. Sociological Methods & Research, 16(1), 155-176.

StataCorp. (2021). Stata Structural Equation Modelling Reference Manual. Release 17. College Station, TX: StataCorp LLC.

In the abstract; The introduction should be rearranged in accordance with the title. The results section could be a little more detailed.

Response: We have augmented results in the Abstract and made the requisite rearrangements.

The introduction section is too long and at some points the integrity of the subject is broken.

Response: We have trimmed the Introduction by ~20% to improve ease of narrative, while also accommodating requests from R2 and R3 to expand certain parts of the Introduction.

In the discussion part; The sentences previously mentioned in the results section are repeated unnecessarily. It is recommended that the title of limitations of the study should be placed just above the conclusion paragraph. In addition, there is a rotavirus paragraph independent of the subject described and discussed in the paragraphs after the limiting features of the study. It is recommended that these parts be removed and rearranged.

Response: We have trimmed the Discussion section and reduced redundancies with the Results. We have also rearranged the Limitations section and placed it before Conclusions. We have also trimmed the paragraph about rotavirus infections and vaccine, while also noting that other Reviewers wanted additional descriptions about the availability of data on rotavirus surveillance (and we therefore added some text on that topic). We hope the Reviewer finds our changes satisfactory.

Although it was mentioned within the limitations of the study, the presence of a table summarizing the sociodemographic characteristics of the children included in the study could have brought the study to a better level.

Response: The HMIS datasets that provided us with information on our outcome variables contain aggregate, district-level information. These datasets do not provide individual-level information about child-specific socio-economic attributes. Hence, we are unable to obtain this information at the individual-level. Given that our unit of analysis is district-year, we have provided aggregate information about district-level socioeconomic attributes in Table 1.

Reviewer: 2
Prof. Heidi Theeten, Universiteit Antwerpen
Comments to the Author:
The subject is interesting in its attempt to disentangle the effect of vaccination and sanitory intervention to reduce infectious disease burden in infants.

Response: We thank the Reviewer for her endorsement.

The manuscript could be improved however, mainly by extending beyond the main hypothesis which is too narrow, and also by considering some more confounder variables.

Response: We now include new supplementary analyses including (1) controlling for Vitamin A supplementation and (2) mediating effect of child undernutrition (stunting among under 5 years old children) in the revised version of the manuscript. These changes appear on pages 11, 12 and appendix Tables A.4 and A.5 of the revised manuscript. They are also included below:

Table R.2: Linear regression predicting Change in Measles as a function of Change in percentage of households with toilets, controlling for change in other covariates including vitamin A supplementation among u5 children and baseline (pre-SBM) annual incidence of measles. (N= 532).

	Coefficient	95% Confidence Interval	
Change in percentage of households with toilets	-0.365*	-0.675	-0.054
Change in percentage of households with electricity	0.149	-0.007	0.306
Change in percentage of households with clean drinking water	-0.197	-0.435	0.041
Change in percentage of households with clean cooking fuel	-0.153	-0.406	0.099
Change in percentage of women with 10th grade or higher education	0.508	-0.024	1.040
Change in percentage of ≤ 1 year old children with measles vaccination	-0.065	-0.277	0.148
Change in percentage of births in hospitals	0.201	-0.066	0.469
Change in percentage of u5 children who received Vitamin A supplementation	-0.190*	-0.365	-0.016

Baseline (pre-SBM) Measles per 1000 u5 children	-0.768***	-0.898	-0.638

*p<0.05, **p<0.01, ***p<0.001*

Table R.3: Relation between change in percentage of households with toilets, change in stunting among under 5 years old children and their effect on change in measles among under 5 years old children estimated using structural equation modelling (N = 532).

Structural Equation Modelling Step 1: ***Direct effect*** of change in percentage of households with toilets on change in percentage of u5 children who are stunted.			
Outcome = Change in percentage of u5 children who are stunted	Coefficient	95% Confidence intervals	
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Change in percentage of women with 10th grade or higher education	-0.214**	-0.329	-0.100
Change in percentage of ≤ 1 year old children with measles vaccination	-0.035	-0.091	0.021
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Change in percentage of households with toilets	-0.320*	-0.617	-0.044
Change in percentage of households with electricity	0.147	0.008	0.286
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Change in percentage of births in hospitals	0.239	0.081	0.558
Change in percentage of u5 children who received Vitamin A supplementation	-0.203	-0.368	-0.038
Baseline (pre-SBM) Measles per 1000 u5 children	-0.772***	0.842	-0.701
Structural Equation Modelling Step 3: ***Indirect effect*** of change in percentage of households on change in measles among u5 children that passes through change in stunting among u5 children			
Outcome = Change in measles among u5 children	Coefficient	95% Confidence intervals	
Change in percentage of households with toilets	-0.042	-0.081	-0.004
Change in percentage of households with electricity	-0.023	-0.065	0.019
Change in percentage of households with clean drinking water	0.023	-0.020	0.065
Change in percentage of households with clean cooking fuel	0.008	-0.009	0.025
Change in percentage of women with 10th grade or higher education	0.002	-0.013	0.016
Change in percentage of ≤ 1 year old children with measles vaccination	0.004	-0.006	0.015
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Structural Equation Modelling Step 4: ***Total effect*** of change in percentage of households on change in measles among u5 children (if there is no mediator in our model)			
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Change in percentage of households with toilets	-0.362*	-0.617	-0.044
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Baseline (pre-SBM) Measles per 1000 u5 children	-0.727***	-0.842	-0.701

**p<0.05, **p<0.01, ***p<0.001*

Step 4 in Table R.3 shows that the total effect coefficient of change in percentage of households with toilets on change in measles among u5 children is -0.362. This is the effect or association we would observe if there was no mediator in our analytic model. The direct effect coefficient of change in percentage of households with toilets on change in measles among u5 children is -0.320, which is smaller than the total effect coefficient (Step 2). The indirect effect of change in percentage of households with toilets on change in measles among u5 children that passes through change in percentage of u5 children who are stunted is -0.042 (Step 3), indicating that stunting may only serve as a partial mediator in this analysis.

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Proportion of total effect mediated = -0.042/-0.362 = 0.116 or about 12%. Put simply, about 12% of the total effect of change in percentage of households with toilets on change in measles among u5 children appears to be mediated by change in stunting among u5 children over our study period.

Introduction

1. The introduction mainly focuses on the role of the sanitation program in preventing ileo-jejunitis and associated immune responses. Another quite evident mechanism is direct infection at shared toilets, which is a possible transmission pathway for measles that is also reduced by the program. This mechanism is not highlighted introduction nor in the discussion.

Response: We agree with the Reviewer that shared toilets may increase direct infections. For this reason, we excluded shared toilets in the formulation of our exposure (i.e. our enumeration of household-level toilet availability only includes un-shared household toilets, in keeping with prior work on SBM and sanitation in India) (Singh, Shah & Bruckner, 2021; Chakrabarti, Singh & Bruckner, 2020). We do not know of any nationally representative sanitation datasets in India that track shared toilet networks or provide household identifiers that share toilets together. Given this data limitation, we are unable to discern whether household clusters that share toilets exhibit infection differentials. We now note this constraint in the Limitations section of our revised Discussion.

References cited:

Singh, P., Shah, M., & Bruckner, T. A. (2021). Child Undernutrition following the Introduction of a Large-Scale Toilet Construction Campaign in India. The Journal of Nutrition, 151(8), 2455-2464.

Chakrabarti, S., Singh, P., & Bruckner, T. (2020). Association of poor sanitation with growth measurements among children in India. JAMA network open, 3(4), e202791-e202791.

2. Line 18: You say "India's abysmal global ranking raises questions about low vaccine effectiveness despite its over 90% immunization coverage following the initiation of the Universal Immunization Program in 2012" – this sentence implies that vaccination coverage is already optimal while in your table 1 it shows vaccination rates of 78-80% for under 1 year old children? This might be rephrased.

Response: We thank the Reviewer for noting this discrepancy and have corrected this statistic (which included polio and other vaccines) to approximately 80% vaccination coverage among ≤ 1year old children, per data reported in the National Family Health Survey (NFHS Round 4, 2017).

Reference cited:

International Institute for Population Sciences (IIPS) and ICF. National Family Health Survey (NFHS-4), 2015-16 . Mumbai: IIPS. 2017. Available from: https://dhsprogram.com/pubs/pdf/FR339/FR339.pdf

3. Small correction: line 51: change "SBM aims" to "SBM aimed", their aim was to have this done by 2019 which has passed already.

Response: We have made this change.

Methods

- On p8 line32 is stated that ratio is reconverted to annual incidence using the number of children reporting any disease. What about children that report no disease? Also, nutrition status is not among the confounders corrected for, which is a pity as it is a strong predictor of immune response. Is no information available on nutrition status of children in India? If this is the case, this limitation should be discussed with its implications.

Response: We apologize for the confusing text. The HMIS data report the relative percentage of VPDs to total reported childhood diseases per district. We converted these percentages to annual incidence of VPDs by following a two-step process. First, we used the number of u5 children reporting ay illness from the AHS, DLHS and NFHS datasets to get the count of u5 children reporting VPDs. Next, we used the population-weighted survey datasets (AHS, DLHS and NFHS) to obtain the counts of u5 children per district, per year. This district-level count of u5 child population was used as the denominator, with the number of u5 children reporting VPDs (estimated in the first step) as the numerator, multiplied by 1000, which yielded our outcome variable. We have now included this detailed explanation in the revised manuscript (page 7, 8).

In addition, per the Reviewer's (and Reviewer 1's) comment about the role of nutrition status, we now include new supplemental analyses that examine the potential mediating role of child undernutrition (stunting among under 5 years old children) on the relation between toilet availability and measles annual incidence. These new analyses are described on page12 and Appendix Table A.5 of the revised analyses. We find that about 12% of the total effect of change in percentage of households with toilets on change in measles among u5 children appears to be mediated by change in stunting among u5 children.

Results:

- Page 12, line 40: When speaking about toilet availability you say that "The most visible improvements occur in Rajasthan"; but above on line 25 you said that no substantial decline in annual incidence of measles was shown in this district. Although you found an overall

decline in measles cases over a period when toilet availability increased, the narrative of this study could be toned down a bit. Factors such as degree of urbanization e.g. were not checked for.

Response: The Reviewer is correct in noting that whereas unadjusted descriptive data presented in the maps suggest rapid increase in toilet availability in Rajasthan, we do not observe a sharp decline in measles in this state. We note that these are descriptive statistics that do not account for other control variables (per our main analyses). We also agree with the Reviewer that we did not examine rural and urban regions within districts separately, owing to non-availability of disaggregated data in the HMIS datasets. However, our analyses control for several key factors that correlate strongly with urbanization (e.g. percentage of households with clean drinking water, electricity, maternal education and hospital births). Whereas explicit examination of rural versus urban regions is not currently feasible with national vaccine preventable diseases surveillance datasets in India, controlling for the variables mentioned above may limit confounding from factors related to urbanization.

Lastly, we understand the Reviewer's suggestion to tone down causal language in the manuscript. We have revised the manuscript to present our findings as more associative than causal (e.g. pages 3, 11, 13), and in particular, augment the Limitations section in the Discussion (p. 15). We hope the Reviewer finds these changes satisfactory.

Discussion

- **Page 13, line 42: you state that "Findings provide proof-of-concept that improvements in ambient sanitation may augment universal immunization efforts in reducing the burden of measles among u5 children in India". This is put a bit too strongly. I suggest to delete proof-of-concept and rephrase this sentence as additional studies are required to really point to an association between the two findings.**

Response: We have made this change.

- **Page 13, line 54: given this study is still observational, I would suggest to delete the phrase "which lends a quasi-experimental design to our analysis"**

Response: John Last's Dictionary of Epidemiology (4th Edition, 2001, Oxford University Press, Oxford) defines quasi-experiment as follows: "A situation in which the investigator lacks full control over the allocation and/or timing of intervention but nonetheless conducts the study as if it were an experiment, allocating subjects to groups. Inability to allocate subjects randomly is a common situation that may be best described as a quasi-experiment."

Per this definition, the key feature of the quasi-experiment is the non-random allocation of subjects to an exposure group, but an analytic treatment of subjects as if it were an experiment. Many observational studies would appear to fall under this definition in that the "allocation" occurs by classifying subjects by exposure level.

In our specific case, given that our exposure (especially the timing) was determined exogenously at a national level and our analysis leverages the timing, scale, and regional variation of this national sanitation campaign, our study design (and our analysis of SBM) would similarly fall under this definition.

However, we understand that readers may find this language unconventional when applied to observational (i.e., not-controlled) studies. We therefore deleted this phrase. As an alternative, we now focus on the elements of the study design that strengthen internal validity and minimize bias.

- measles annual incidence decrease on its own is expected to have an impact on other (vaccine preventable) infections, as measles induces immune depression. Has this effect been taken into account? Please discuss on this issue as well.

Response: As the Reviewer notes, there may be a reciprocal relation between measles and other vaccine preventable infectious diseases (i.e., either may exacerbate the other). Given that measles and other infectious diseases may also be caused or exacerbated by inadequate sanitation, controlling for measles may introduce collider bias (per logic from Directed Acyclic Graphs) and induce potentially spurious relations between the exposure and outcome. For this reason, we do not control for measles when analyzing other vaccine preventable diseases (and vice-versa) in our analysis.

Conclusion

- Should be rephrased and toned down. From the results it is clear that there is only a small reduction in measles cases (decrease of 1.12 measles cases for a 7% increase in household with toilets)

Response: We have modified this Conclusion accordingly to note that it is “small”. We also expand the Limitations section in the Discussion.

Appendix Table A.3:

- It says “%age” in the table, this seems incorrect

Response: We have changed this to “district-level percentage of households with toilets”. We hope the Reviewer finds our changes satisfactory.

Reviewer: 3
Dr. Kristien Verdonck, Institute of Tropical Medicine
Comments to the Author:
This manuscript addresses an interesting topic, uses relevant data, and is written clearly and transparently.

Response: We thank the Reviewer for her endorsement.

Nevertheless, as explained below, I have some concerns about the authors’ claim that the study provides proof-of-concept that improvements in sanitation augment immunization efforts in reducing the burden of measles in India.

Major comments

- A before-after comparison as only argument is not sufficient to claim ‘proof of concept’ (in my opinion). What if the incidence of measles is steadily decreasing over the years? What if there was a measles outbreak in 2013? If that were the case, the incidence would decrease after 2013 regardless of the intervention. Although the authors did adjust their analysis for potentially confounding factors, I am not convinced that all relevant confounding is captured. The addition of other arguments could make the case more convincing, for example spatial arguments (districts with good sanitation have less vaccine-preventable diseases than districts with poor sanitation at any point in time). The addition of intermediary factors (such as toilet use, malnutrition, environmental enteropathy) could also help.

Response: We note that two Reviewers objected to the use of the term “proof-of-concept.” We, therefore, have deleted this phrase throughout the manuscript and instead use associational language to describe the findings.

The Reviewer is also correct in noting that exceedingly high (or low) cases in a previous year may “rebound” thereafter. This statistical phenomenon, also referred to as regression to the mean, may lead to incorrect inference for our study which involves two time points. For this reason, throughout our analyses, we controlled for pre-SBM or ‘baseline’ disease annual incidence in our study.

We further agree that spatial clustering may induce variations in both the exposure and outcome and that districts within a region or state may be more similar to each other. For this reason, we have included clustered standard errors (districts clustered by states) in our analyses.

In addition, per the Reviewer’s suggestion, in the revised version we now present several new supplementary analyses. We now include vitamin A supplementation as a new covariate (Appendix Table A.4). We have also performed mediation analysis with an indicator of child undernutrition (stunting among under 5-year old children) (Singh, Shah & Bruckner, 2021) using structural equation modelling. The results from these analyses are presented on page 12 and in Appendix Table A.5. Our original inference remains essentially unchanged and we note that about 12% of the total effect of change in percentage of households with toilets on change in measles among u5 children appears to be mediated by change in stunting among u5 children. We, however, did not have data on the other intermediary factors and therefore list this data limitation in the Discussion.

Reference cited:

Singh, P., Shah, M., & Bruckner, T. A. (2021). Child Undernutrition following the Introduction of a Large-Scale Toilet Construction Campaign in India. The Journal of Nutrition, 151(8), 2455-2464.

- Only two time points (2013 and 2016) are included in the evaluation. What about yearly variation in the frequency of vaccine-preventable diseases? Considerations of variability over the years are relevant (and I understand from the methods’ section that this information is available?). In the case of measles, as the authors recognise: “the highly contagious nature of measles (relative to diphtheria, pertussis and tetanus) may impart greater amenability to change, following SBM.” But the amenability to change is also possible regardless of SBM?

Response- The HMIS data do not span beyond 2012, which limits our ability to model stable historic trends. The Reviewer is correct in noting that inherent attributes of districts may predispose certain districts to sustain high or low disease incidence over time. We accounted for these inherent attributes, also referred to as district intercepts or “fixed effects” (econometric definition per Wooldridge, 2010) by differencing out latent factors that remain stable within districts over our study period (i.e., post-SBM values minus pre-SBM values). Our approach of taking first differences adjusts for such district-specific attributes by focusing on the *change* in outcome with respect to *change* in exposure, rather than fixed attributes that may influence both the outcome and the exposure. Furthermore, our inclusion of baseline or pre-SBM disease annual incidence also reduces the likelihood of incorrect inference arising from regression to the mean.

We agree with the Reviewer that the amenability of measles to rapid change may exist independent of SBM. This change would potentially occur as a function of change in vaccination rates (which we include as a covariate), health infrastructure (indicated by hospital or institutional births in our analysis), maternal socioeconomic attributes (e.g., maternal education), and general economic prosperity (e.g., availability of clean drinking water, clean cooking fuel and electricity). In our revised analyses, we also include vitamin A supplementation, in addition to a comprehensive list of controls described above that account for factors which may underlie change in measles incidence across districts in India. However, we understand that the possibility of residual confounding cannot be ruled out. We acknowledge this point in the Limitations section of the revised Discussion (p.15).

References cited:

Wooldridge, J. M. (2010). Econometric analysis of cross section and panel data. MIT press.

- I believe that there are more limitations. Example 1: is there any indication (in the present study) of toilet use and of improvement of nutritional status due to the intervention? As the authors do not present data about such intermediary steps, we can only speculate on how exposure and outcome are linked.

Response: See our earlier response regarding the data limitation on some of these variables and on the new supplemental analysis using structural equation modelling to examine the direct and indirect relation between toilet availability and measles annual incidence with child stunting serving as the mediator. As with most ecological analyses, we do not have full information on mechanistic "intermediary steps" and therefore list this limitation in the Discussion (p.14, 15).

Example 2: the data about the exposure before and after the intervention comes from different sources. How could this affect the findings?

Response: In theory, retrieving exposure from two different sources could introduce measurement error. To assess this possibility. We examined multiple published studies that have used DLHS4, AHS and NFHS4 datasets (collectively) and we found no description of systematic measurement error in any of these surveys (Geldsetzer et al, 2018; Jung et al, 2019; Dandona et al, 2016; Singh, Shah & Bruckner, 2021). The toilet and sanitation component was identical across all three surveys as is also described in official documentation of survey design and methodology for each of these surveys (Office Of The Registrar General & Census Commissioner. 2014a, 2014b; IIPS 2014, 2017). The sampling methodology of each of these surveys, per published reports (Office Of The Registrar General & Census Commissioner. 2014a, 2014b; IIPS 2014, 2017), shows that these surveys were designed to be representative at the district level, following the same sampling frame and sample selection protocols.

We also note that, for measurement error to induce the pattern of results we report, district-level measurement of the toilet and sanitation component would have to be systematically over-reported only in regions with low (but not high) measles incidence, and only for 2016 but not for the 2013 wave. We know of no reports that have raised concerns about the validity of aggregate estimates from the NFHS, AHS or the DLHS—and it seems implausible that measurement error of toilet and sanitation would be systematic with respect to measles incidence in 2016 but not in 2013.

For our study, we have used the most comprehensive district-representative, national surveys on child anthropometry available in India (over our study period). We do not know of any reports in peer-reviewed research articles or by government and/or policy-making agencies that have identified discrepancies in these surveys.

References cited:

Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Danaei G, et al. Geographic and sociodemographic variation of cardiovascular disease risk in India: A cross-sectional study of 797,540 adults. PLOS Med . 2018 Jun 19;15(6):e1002581. Available from: https://doi.org/10.1371/journal.pmed.1002581

Jung L, De Neve J-W, Chen S, Manne-Goehler J, Jaacks LM, Corsi DJ, et al. Nationally representative household survey data for studying the interaction between district-level development and individual-level socioeconomic gradients of cardiovascular disease risk factors in India. Data Br . 2019 Sep 13;27:104486. Available from: https://pubmed.ncbi.nlm.nih.gov/31720318

Dandona R, Pandey A, Dandona L. A review of national health surveys in India. Bull World Health Organ. 2016;94(4):286.

Singh, P., Shah, M., & Bruckner, T. A. (2021). Child Undernutrition following the Introduction of a Large-Scale Toilet Construction Campaign in India. The Journal of Nutrition, 151(8), 2455-2464.

Office Of The Registrar General & Census Commissioner. 2014a. Annual health survey report a report on core and vital health indicators. Ministry of Home affairs, Government of India. Available at: https://www.censusindia.gov.in/vital_statistics/AHS/AHS_report_part1.pdf

Office Of The Registrar General & Census Commissioner. 2014b. Annual Health Survey. Clinical, Anthropometric & Bio-Chemical (CAB)-2014. Available at: https://www.censusindia.gov.in/2011census/hh-series/HH-2/CAB-Introduction.pdf

International Institute for Population Sciences (IIPS). 2014. District level household & facility survey (DLHS-4). Available at: http://rchiips.org/DLHS-4.html

International Institute for Population Sciences (IIPS) and ICF. 2017. National Family Health Survey (NFHS-4), 2015-16: India. Mumbai: IIPS. Available at: https://dhsprogram.com/pubs/pdf/FR339/FR339.pdf

- The authors mention the quasi-random nature of the SBM programme. What is meant exactly and how does this affect the authors' before-after comparison? How is this a strength of the study?

Response: Given that our exposure was determined exogenously at a national level and our analysis leverages the precise timing and scale of this national sanitation campaign, we contend that the timing and scale of the exposure is not determined by each specific district. One could therefore view the exposure as have an element of random assignment to districts. This exogenous exposure, despite not being truly randomly "assigned" by the investigator, limits the possibility of (1) a "common cause" driving both the outcome and the exposure, (2) establishes temporal order in that the exposure (SBM) precedes the outcome, and (3) is not "caused" by district-level variations in the outcome. These attributes reduce inferential threats from selection bias and potential reverse causation.

Per the Reviewer's question, we now list briefly these three aspects of the study design in the Introduction, which strengthen internal validity.

- The authors do not discuss two issues that may affect the findings. (1) Spatial considerations/dependency (do districts that are near resemble each other more than districts that are far away?) and (2) Statistical instability (is the number of cases small in some (small) districts so that small changes in the number of cases (a few cases more or less) have a large effect on the annual prevalence/incidence?).

Response: We do not have *a priori* expectations of the range of radii from district centroids that would appropriately capture similar or dissimilar districts in a region. Given that some states such as Goa, Delhi or northeastern states are substantially smaller than others like Uttar Pradesh, Rajasthan or Maharashtra, we did not include uniform spatial proximity estimates in our analysis. It is plausible to conduct such an exercise potentially with block-level data (analogous to census tracts in the US), but we do not know of national disease surveillance databases that report block-level estimates. We now acknowledge this limitation in the revised manuscript (Limitations section in Discussion). In addition, to guard against non-independence of district-level observations within states, we cluster standard errors by state in all our analyses.

The Reviewer is also correct in questioning whether our results are driven by influential outliers. To that end, we now include two additional robustness checks wherein we (1) log transform the change in measles (outcome) to reduce the effect of potential outliers and re-estimate equation 1, and (2) z-scale the outcome, remove observations beyond ± 3 standard deviations and re-estimate equation 1. Results from these analyses are now included in Appendix Tables A.6 and A.7 and are also presented below. Removal and/or adjustment for outliers does not alter our original inference.

Table R.4: Linear regression predicting log transformed change in measles as a function of change in percentage of households with toilets, controlling for change in other covariates and baseline (pre-SBM) annual incidence of measles (N = 532).

	Coefficient	95% confidence intervals	
Change in percentage of households with toilets	-0.013*	-0.023	-0.003
Change in percentage of households with electricity	0.004	-0.001	0.009
Change in percentage of households with clean drinking water	-0.002	-0.004	0.000
Change in percentage of households with clean cooking fuel	-0.006	-0.014	0.002
Change in percentage of women with 10th grade or higher education	0.003	-0.003	0.009
Change in percentage of ≤ 1 year old children with measles vaccination	-0.001	-0.003	0.001
Change in percentage of births in hospitals	0.002	-0.002	0.005
Change in percentage of u5 children who received Vitamin A supplementation	-0.003	-0.008	0.003
Baseline (pre-SBM) Measles per 1000 u5 children	-0.027***	-0.042	-0.011

**p<0.05, **p<0.01, ***p<0.001*

	Coefficient	95% confidence intervals	
Change in percentage of households with toilets	-0.007*	-0.011	-0.002
Change in percentage of households with electricity	0.001	-0.002	0.004
Change in percentage of households with clean drinking water	-0.002	-0.006	0.003
Change in percentage of households with clean cooking fuel	-0.004	-0.008	0.001
Change in percentage of women with 10th grade or higher education	0.000	-0.008	0.008
Change in percentage of ≤ 1 year old children with measles vaccination	-0.001	-0.006	0.003
Change in percentage of births in hospitals	0.006	0.001	0.011
Change in percentage of u5 children who received Vitamin A supplementation	-0.002	-0.006	0.002
Baseline (pre-SBM) Measles per 1000 u5 children	-0.027***	-0.035	-0.018

Table R.5: Linear regression predicting z-scaled change in measles as a function of change in percentage of households with toilets, controlling for change in other covariates and baseline (pre-SBM) annual incidence of measles (restricted to outcome distribution within ±3 standard deviations or z scores of -3 to +3). (N = 509)

**p<0.05, **p<0.01, ***p<0.001*

- P12, first paragraph and appendix table A.1. Why was this approach used and what is the main message? Does it mean that the largest changes in outcome were seen in the (few) districts with the most extreme exposure levels? Is it possible that this table reflects statistical instability?

Response: We included Appendix Table A.1 to give readers a sense of the distribution of the outcome in our analytic dataset. This approach was purely intended as a descriptive exercise. We can remove this Table if the Reviewer feels that it confuses the average reader. Also, per the comment about instability, please see our previous response regarding robustness of results to exclusion of outliers.

- What was the effect of the inclusion of candidate confounders on the coefficient (beta1)? Which variables had the largest effect?

Response: In our revised analyses (including vitamin A supplementation as a covariate), change in percentage of u5 children who received Vitamin A supplementation and Baseline (pre-SBM) Measles per 1000 u5 children showed statistically detectable, inverse relations with change in measles among u5 children. These results are presented in Appendix Table A.4 and also appear below:

Table R.6: Linear regression predicting Change in Measles as a function of Change in percentage of households with toilets, controlling for change in other covariates including vitamin A supplementation among u5 children and baseline (pre-SBM) annual incidence of measles. (N= 532).

	Coefficient	95% Confidence Interval	
Change in percentage of households with toilets	-0.365*	-0.675	-0.054
Change in percentage of households with electricity	0.149	-0.007	0.306
Change in percentage of households with clean drinking water	-0.197	-0.435	0.041
Change in percentage of households with clean cooking fuel	-0.153	-0.406	0.099
Change in percentage of women with 10th grade or higher education	0.508	-0.024	1.040
Change in percentage of ≤ 1 year old children with measles vaccination	-0.065	-0.277	0.148
Change in percentage of births in hospitals	0.201	-0.066	0.469

Change in percentage of u5 children who received Vitamin A supplementation	-0.190*	-0.365	-0.016
Baseline (pre-SBM) Measles per 1000 u5 children	-0.768***	-0.898	-0.638

**p<0.05, **p<0.01, ***p<0.001*

- Could Vitamin A supplementation (which increased during the study period) be a confounding factor?

Response- We now include change in Vitamin A supplementation among under 5 years old children as a supplemental analysis in the revised manuscript. Results from this analysis (presented above and in Appendix Table A.4) indicate an inverse association between change in Vitamin A supplementation and change in measles among under 5 years old children. However, the toilet coefficient remains robust to inclusion of the Vitamin A variable.

Minor comments

- The paragraph on ‘what is already known’ suggests that the study will estimate the strength of the association between open defecation, child malnutrition and vaccine efficacy. The study does not really fill this gap, as it only looks at self-reported availability of toilets and publicly reported (notified) cases of four vaccine-preventable diseases.

Response: In the revision, we now align the text in this section with our study objectives. Thank you for catching this inconsistency.

- Abstract and introduction. “India consistently reports the most diphtheria, pertussis, tetanus and measles cases worldwide.” This is not surprising given the large population size of India. I consider that the incidence per 100,000 (or per 1000) inhabitants per year would be a more interesting measure of disease frequency.

Response: We have revised the Introduction to include mortality (standardized by population) from VPDs among u5 children- “Between 2000 and 2020, the annual incidence of these diseases among under 5 year old (u5) children in India averaged 32.8 for measles, 3.5 for diphtheria, 31.1 for pertussis and 3.3 for tetanus per 100,000 population.(WHO, 2020)”

- Introduction. ‘High burden of child mortality from VPDs’. How high is this burden? Any references for incidence of infections and deaths per population?

Response: We now include estimates of this burden from Liu et al., (2012) in the revised Introduction where we say, “In 2010, measles accounted for about 3% of all under 5 deaths in the India (Liu et al, 2012; WHO, 2020). Tetanus accounted for approximately 20 deaths per million live births during the same time period (Fadel et al, 2017), contrasting sharply with other low and middle income countries that exhibit substantially lower under 5 mortality from VPDs (Liu et al, 2012).”

References cited:

Liu, L., Johnson, H. L., Cousens, S., Perin, J., Scott, S., Lawn, J. E., ... & Child Health Epidemiology Reference Group of WHO and UNICEF. (2012). Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. The Lancet, 379(9832), 2151-2161.

Fadel, S. A., Rasaily, R., Awasthi, S., Begum, R., Black, R. E., Gelband, H., ... & Jha, P. (2017). Changes in cause-specific neonatal and 1–59-month child mortality in India from 2000 to 2015: a nationally representative survey. The Lancet, 390(10106), 1972-1980.

World Health Organization (WHO). (2020). WHO vaccine-preventable diseases: monitoring system. 2020 global summary. Available at: https://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=IND&%20commit=OK

- The outcome of interest is the change in annual incidence of four vaccine-preventable diseases at district level. I consider that in this context, "annual incidence" is a more appropriate description of disease frequency than "annual prevalence".

Response: We agree with the Reviewer that our analyses pertain to annual incidence rather than annual prevalence of VPDs. We have revised the manuscript throughout to reflect this change.

- Does the environmental enteropathy occur at the age at which infants/children are vaccinated for the four vaccine-preventable diseases? Any references supporting this?

Response: Scholars note that environmental enteropathy poses a key risk to child development starting from a very early age (first 1000 days of life) (Black et al, 2008; Victora et al, 2010; Grantham-McGregor et al, 2007; Syed, Ali & Duggan, 2016; Budge at al, 2019). Some researchers have also posited potential *in utero* changes in the fetus related to maternal environmental enteropathy (Lauer et al, 2018). Whereas environmental enteropathy can manifest at any age, it presents grave concerns particularly among under 5-year old children (Black et al, 2008). These include neonates, infants, as well as older children (Black et al, 2008). We now include this information in the revised manuscript's Introduction (page 5).

References cited:

Black, R. E., Allen, L. H., Bhutta, Z. A., Caulfield, L. E., De Onis, M., Ezzati, M., ... & Maternal and Child Undernutrition Study Group. (2008). Maternal and child undernutrition: global and regional exposures and health consequences. The lancet, 371(9608), 243-260.

Victora, C. G., De Onis, M., Hallal, P. C., Blössner, M., & Shrimpton, R. (2010). Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics, 125(3), e473-e480.

Grantham-McGregor, S., Cheung, Y. B., Cueto, S., Glewwe, P., Richter, L., Strupp, B., & International Child Development Steering Group. (2007). Developmental potential in the first 5 years for children in developing countries. The lancet, 369(9555), 60-70.

Syed, S., Ali, A., & Duggan, C. (2016). Environmental enteric dysfunction in children: a review. Journal of pediatric gastroenterology and nutrition, 63(1), 6.

Budge, S., Parker, A. H., Hutchings, P. T., & Garbutt, C. (2019). Environmental enteric dysfunction and child stunting. Nutrition reviews, 77(4), 240-253.

Lauer, J. M., Duggan, C. P., Ausman, L. M., Griffiths, J. K., Webb, P., Agaba, E., ... & Ghosh, S. (2018). Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda. The American journal of clinical nutrition, 108(4), 889-896.

- P7 ‘thus far’: It is unclear to the reader when this was written.

Response: We have changed this to 2019.

- P11. Why did the authors expect that errors would be correlated?

Response: We expected errors to be correlated across districts within a state owing to social, demographic, economic and administrative factors that may render districts within a state to be more similar to each other than to those of other states. To account for this non-independence, we specified cluster-robust standard errors (clustered at the state level). We have now included this information in the revised manuscript (page 9, 10).

- Table 1. The authors present the difference of two means (before-after). The mean of the differences (for all the districts) may be more appropriate here?

Response: We apologize for presenting Table 1 in a confusing manner. The Change column presents mean of the differences (rather than difference of means) for all the districts in our data (Post-SBM minus Pre-SBM). We have now added this clarification in the revised Table 1.

- Figure 1 and 2. A two-colour scale would be clearer (one colour for increase and another colour for decrease).

Response: We have made this change.

- Equation 1. Regarding the term with beta2. I wonder if the authors considered using a mixed model. Is this term with beta2 used as an equivalent of a random effect per district? I wondered if there is any advantage of the approach in equation 1 over a mixed model with a random effect?

Response: The leading econometric author in this area recommends using a fixed effects approach when examining longitudinal outcomes with time-varying exposures (Wooldridge, 2010). Using a pre-post (change) analysis offers an intuitive way to remove time invariant, endogenous attributes of districts (or district fixed effects) that, if not accounted for, may limit comparability (and statistical exchangeability) across our units of analyses. Random effects or mixed effects models do not provide this benefit as they only model the variance of unit means from a grand mean, but not the actual ‘intercept’, making them better-suited for exposures that do not vary substantially over time (Wooldridge, 2010; Hausman, 1978).

References cited:

Wooldridge, J. M. (2010). Econometric analysis of cross section and panel data. MIT press.

Hausman, J. A. (1978). Specification tests in econometrics. Econometrica: Journal of the econometric society, 1251-1271.

- I was surprised to find that none of the authors has an affiliation with an institute in India.

Response: The Reviewer is correct. That stated, our team is well-versed in the datasets used and of the India sanitation and open defecation context. Dr. Manisha Shah has multiple studies and ongoing randomized controlled trials that examine sanitation, child health and child education-related outcomes in India. Dr. Parvati Singh is a resident of India and has led state-level World Bank programs focusing on maternal and child health in rural regions. Dr. Donald Forthal has served as a physician in India, specializing in tropical infectious diseases in this population. Dr. Tim Bruckner has conducted research on health outcomes in India and has collaborated extensively with the World Health Organization with emphasis on healthcare planning in developing countries.

VERSION 2 – REVIEW

REVIEWER	Verdonck, Kristien Institute of Tropical Medicine
REVIEW RETURNED	15-Feb-2022

GENERAL COMMENTS	The authors have addressed the concerns formulated by the three reviewers and revised the manuscript accordingly. A very minor comment: I think that in Appendix Table A.5, in the line about Structural Equation Modelling Step 3, the term "with toilets" is missing.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Dr. Kristien Verdonck, Institute of Tropical Medicine
Comments to the Author:
The authors have addressed the concerns formulated by the three reviewers and revised the manuscript accordingly. A very minor comment: I think that in Appendix Table A.5, in the line about Structural Equation Modelling Step 3, the term "with toilets" is missing.

Authors' Response: We thank the Reviewer for their endorsement. We have made the requisite correction in Appendix Table A.5.