Title: The use of mediation analysis in evaluation of complex health interventions

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The use of mediation analysis in evaluation of complex health interventions

Abstract

This paper presents an application of the causal inference approach to mediation analysis using the example of a complex intervention that aimed to improve the quality of care at health centres in Uganda. Mediation analysis is a statistical method that aims to isolate the causal mechanisms that make an intervention work in a given context. We combined data from a cluster randomized control trial and a mixed-methods process evaluation. We developed two causal models following our hypotheses of how the intervention was intended to work through mechanisms at health centres to improve health outcomes in the community. In adjusted analyses, there was evidence an effect of the intervention on some health centre mechanisms; however, these did not lead to improvements in community health outcomes. We discuss the practical and epistemological challenges encountered when using mediation analysis to evaluate a complex intervention. These findings will inform future evaluations.

Trial registration

The trial reported in this manuscript is registered at: [details omitted for double-anonymized peer review]

Keywords

mediation analysis, complex interventions, evaluation, global health, logic model, cluster randomised control trial, process evaluation, malaria

Background

The randomised control trial (RCT) remains the leading study design to determine the overall effect of an intervention – that is, whether the intervention works, or not (Craig et al., 2008; Skivington et al., 2021). However, with increasing recognition of complexity in intervention design and evaluation of health programmes, it is critical that we also learn the causal mechanisms that make an intervention work in a given context (Moore et al., 2015). Knowing the effect of mechanisms can be considered as important as the overall outcome of the RCT (Lee et al., 2019). Mechanisms signal promising intervention components that can be refined, adapted, or discarded to improve implementation and amplify the impact of future interventions (Hafeman and Schwartz, 2009; Jamal et al., 2015). As part of the wider methodology of causal inference, mediation analysis is a statistical method that can isolate specific mechanisms on the causal pathway between the intervention and the outcome (Emsley et al., 2010). It is an approach that is promoted within evaluation research especially for complex interventions that have several interacting components (Bonell et al., 2012; Moore et al., 2015).

Mediation analysis identifies causal mechanisms, referred to as mediators, by separating the effect of an intervention into ‘direct’ and ‘indirect’ effects (Emsley et al., 2010). The direct effect estimates how much the intervention works through all variables except the specific mediator under investigation. The indirect effect, also known as the mediating effect, estimates how much of the intervention works through a specific mediator, Figure 1. Because the indirect effect isolates the effect of an individual mediator, it can identify effective causal pathways even if the overall outcome

of the RCT is not successful (Whittle et al., 2017). Mediation analysis also has the potential to combine multiple pathways in a single model (Hennessy and Greenberg, 1999; Lipsey and Pollard, 1989; Vadrucci et al., 2016).

Mediation analysis is recognized as having two broad approaches: statistical and causal. Statistical mediation analysis, popularized by Baron and Kenny's (1986) seminal work, uses a structural equation modelling framework of linear regression models to estimate mediated effects. This approach is promoted in the popular Medical Research Council (MRC) guidance on process evaluations of complex interventions (Moore et al., 2015), and in studies referencing the MRC guidance (Gardner et al., 2010; Littlecott et al., 2014). However, recent methodological advancements have shown that the statistical approach is limited to linear models and does not sufficiently address confounding along the causal pathway (Imai, Keele and Tingley, 2010; Nguyen et al., 2021). Causal mediation analysis is an alternative approach using Rubin's counterfactual casual inference framework to identify mediators and accommodate issues of confounding (Imai, Keele and Tingley, 2010). There are few applications of causal mediation analysis to complex health care interventions, especially those implemented in low resource settings (Anselmi et al., 2017). It is not yet clear if additional considerations are needed when applying the method to interventions in low resource settings as we have seen necessary for the randomised trial (English et al., 2011; Okwaro et al., 2015; Ranson et al., 2006).

Here we present an application of the causal inference approach to mediation analysis using the example of a complex intervention implemented in rural Uganda. The intervention (PRIME) aimed to improve quality of care for malaria and other febrile illness at public health centres. A cluster RCT and mixed methods process evaluation examined the impact and implementation of the intervention (Chandler et al., 2013; Staedke et al., 2013). In this paper, we investigate whether health center mechanisms hypothesised to be addressed by the intervention had an effect on malaria-related health outcomes of community children. We also consider our experiences of using causal mediation analysis including the accommodations we made to fit the method, and how this influenced our interpretation of results.

Methods

Study setting

The cluster RCT and process evaluation were conducted in Tororo district, Uganda, from 2010-2013. At the time of the study, the burden of malaria in Uganda was high and health system challenges limited access to accurate diagnosis and prompt effective antimalarial treatment (Jagannathan et al., 2012; Kyabayinze et al., 2012; Yeka et al., 2012). Use of malaria rapid diagnostic tests **(**mRDTs**)** to target antimalarial treatment and improve health outcomes were strongly advocated and were being scaled-up across Africa (Hopkins et al., 2009; World Health Organization, 2012), but had not yet been introduced into the public health care system in Uganda. In Tororo, there was an exceptionally high malaria transmission during the years leading up to and throughout the study period (Kilama et al., 2014). Health infrastructure in the area remains limited.

Most lower-level public health centres lack electricity and running water, have inconsistent availability of supplies and medications, and are generally understaffed. Very few households in the study area have electricity (1%) and education levels are low (Staedke et al., 2016).

The intervention included three training strategies for health workers: 1) fever case management using mRDTs, 2) patient-centered services, and 3) health center management. It also ensured the availability of mRDTs and artemether-lumefantrine (AL), the recommended first line antimalarial therapy for malaria in Uganda, when health centre stocks ran low. By addressing the barriers to providing good quality care for malaria and febrile illnesses, the intervention aimed to improve appropriate malaria case management and patient satisfaction, leading to repeat attendance at health centres, and ultimately, improved health outcomes in community children (DiLiberto et al., 2015). An examination of the intervention design process and intervention components has been reported elsewhere (DiLiberto et al., 2015).

The cluster RCT assessed the impact of the intervention, compared to the current standard of care, on the prevalence of anemia (an established proxy for malaria-associated health outcomes) in children under 5 and 5-15 years of age (Staedke et al., 2013**)**. Twenty public health centres were included with 10 randomised to the intervention and 10 to the current standard of care. Cross-sectional community surveys were conducted at baseline and annually for two years (year 1: N=8,766; year 2: N= 8,766). Households within 2km of the health centres formed the sampling frame for the

survey and were randomly selected for recruitment into the survey. The primary outcome was prevalence of anaemia (haemoglobin <11g/dL) in children under five and 5 to 15 years. The process evaluation assessed implementation processes, mechanisms, and context of the PRIME intervention (Chandler et al., 2013). Methods included patient exit interviews with caregivers of children under five conducted at all health centres at baseline and annually for two years (year 1: N=107; year 2: N= 100), and questionnaires with health workers stationed at each health centre conducted between 9 and 12 months after the intervention started (N=49). Additionally, health centre surveillance of outpatient records and stocks of mRDTs and AL was conducted at all health centres for 17 months during the study period.

Mediation analysis

We employed the causal inference approach to mediation analysis advanced by Imai et al (2010) to explore the effect of health centre mediators on community health outcomes in three steps: 1) identification of mediator variables and pathways, 2) estimation of direct effects, and 3) estimation of indirect effects.

1) Identification of mediator variables and pathways

We used the PRIME intervention logic model and theory of change as the theoretical basis to guide the selection of mediator variables and explain how they are related to the outcomes, Figure 2. We identified data from across the cluster RCT and process evaluation to translate this theoretical model into causal pathways with variables suitable for mediation analysis. These variables included: health worker attitude, patient

satisfaction, appropriate treatment of fever, and health centre stocks of malaria medication and diagnostics. The data sources and collection procedures for the variables are outlined in Table 1.

We arranged the variables into two causal pathways following the conventions for mediation analysis which requires a forward and chronological pathway from the exposure through the mediators and towards the outcome (Greenland et al., 1999). The variables were arranged following our hypotheses of how the intervention was intended to work to improve outcomes at the health centre level, and ultimately improve health outcomes in the community. We conducted a descriptive statistical analysis of each variable and health centre characteristics.

2) Estimation of direct effects

We estimated the direct effects to identify which mediators had a statistically significant association with the intervention. We estimated the direct effect of the intervention on each individual mediator variable using an intention-to-treat analysis. The mediators were calculated as mean scores at the health centre level. Where the score was a proportion, the means were far from the bounds of 0 and 100%; therefore, linear regression were acceptable. A series of linear regression models was performed to test the effect of the intervention on each potential mediator. Individual crude analyses were followed by analyses adjusted for health centre monthly average patient load and number of health workers stationed at the health centre.

3) Estimation of indirect (mediated) effects

We estimated indirect effects along the two causal pathways to quantify the portion of the intervention that works through the mediator variables. We used the Stata 'mediation' package designed specifically for mediation analysis based on the potential outcomes framework (Hicks and Tingley, 2011). Within the package, the 'medeff' command fitted an algorithm of regression models, in this case a continuous mediator and continuous outcome variables. Model parameters were simulated from their sampling distribution to determine the indirect effect, the direct effect, and the total effect of the intervention on the outcome of interest. Summary statistics including mean point estimates and confidence intervals were produced. Individual crude analyses of the effect of each pathway were followed by analyses adjusted for health centre monthly average patient load and number of health workers stationed at the health centre.

A second command, 'medsens', is available to run a sensitivity analysis of the results. The sensitivity analysis investigates potential unmeasured confounding along the causal pathway between the intervention and outcomes, and between the mediator and outcomes. The analysis is necessary for results to have a causal interpretation (Hicks and Tingley, 2011).

All analyses were done using Stata version 12 (STATA Corp Lp, College Station, Tx).

Results

1) Identification of mediator variables and pathways

The two causal pathways with mediator variables and outcomes are shown in Figure 3.

The first pathway traces the hypothesis that the intervention would lead to improved stocks of AL and mRDTs, and these mediators would lead to improved health centre outcomes of health worker attitude, patient satisfaction and appropriate treatment of fever, Table 2.

The second pathway traces the hypothesis that the intervention would improve health worker attitude, patient satisfaction, appropriate treatment of fever, and stocks of AL and mRDTs, and through each of these mediators there would be a decrease in prevalence of anaemia in community children. Because the mediators of health worker attitude, patient satisfaction and appropriate treatment of fever were assessed just after the midline community survey was completed, only the outcome from the final community survey was used to maintain chronological ordering of the exposure-mediator-outcome variables to avoid chances of reverse causation in the analysis. However, because stocks of AL and mRDTs were collected continuously from baseline, it was possible to include these as mediators of the health outcome from both the midline and final community survey. Additionally, because assessment of patient satisfaction and appropriate treatment of fever was only conducted with children under 5 years of age, we limited the outcome of prevalence of anaemia to children under 5 for the pathways with these mediators, Table 2.

Health centre characteristics demonstrate that average monthly patient load and number of health workers stationed at each health centre were similar between health centres in each study arm Table 3. Average monthly patient load was 194 in the standard care arm and 203 in the intervention arm. Average number of health workers stationed at the health centres was 2.7 in the standard care arm and 2.6 in the intervention arm.

Scores for health worker attitude, patient satisfaction and appropriate treatment of fever were similar between health centres in each study arm, Table 4. Health worker attitude scores were 45% in the standard care arm and 50% in the intervention arm suggesting that health workers had slightly more positive attitudes regarding their motivations and feelings towards their work in the intervention arm. Patient satisfaction scores were similar between arms at 82% in the standard care arm and 83% in the intervention arm suggesting that overall patients were satisfied with their experiences at the health centre. Appropriate treatment scores were also similar between arms at 72% in the standard care arm and 75% in the intervention arm suggesting that overall health workers were appropriately treating around three quarters of children under 5 years presenting at the health centre with a fever.

In both time periods, total duration of stock-outs of any package size of AL in months was similar between trial arms – 8.4 months in the standard care arm and 7.76 months in the intervention arm between baseline and the midline community survey, and 18.56 months in the standard care arm and 17.45 months in the intervention arm in between

baseline and the final community survey, Table 4. There were no periods of complete stock-out of all AL packages at any health centres during the study period.

In both time periods, total duration of mRDT stock-outs in months was different between trial arms – 4.78 months in the standard care arm and 0.67 months in the intervention arm between baseline and the midline community survey, and 7.61 months in the standard care arm and 1.4 months in the intervention arm in between baseline and the final community survey, Table 4. In the first time period, some health centres had 0 months stock-out of mRDTs.

2) Direct effects

There was weak evidence of a difference in health worker attitude scores, with on average 5 percentage points (CI -0.01, 0.11) higher scores in the intervention health centres compared to the standard care health centres. After adjusting for monthly average patient load and number of health workers stationed at the health centre, health worker attitude scores were 6 percentage points (CI -0.01, 0.12) higher in the intervention arms, Table 5. In the period between the baseline and midline community survey, after adjusting for monthly average patient load and number of health workers stationed at the health centre, there was strong evidence of shorter periods of stock-outs of mRDTs (an average of 5.96 months fewer, CI -9.66, -2.26) in the intervention health centres compared to the standard care health centres, Table 5. In the period between the baseline and final community survey, after adjusting for monthly average patient load and number of health workers stationed at the health centre, there was

strong evidence of an average of 4.46 months fewer stock-outs of mRDTs (CI -7.46, -1.46), Table 5. There was no evidence of an effect of the intervention on the other mediators of patient satisfaction and appropriate treatment of fever; therefore, these were not included in the estimation of indirect effects.

3) Indirect (mediation) effects

For the first pathway analysed, there was no evidence of a causal pathway between the intervention and health worker attitude, patient satisfaction and appropriate treatment of fever mediated by health centre stocks of AL or mRDTs, Table 6.

For the second pathway analysed, there was no evidence of a causal pathway between the intervention and prevalence of anaemia mediated by either health worker attitude or health centre stocks of mRDTs, Table 7. Even though there appears to be evidence of a total effect of the intervention on community health outcomes mediated by health centre stocks of AL and mRDTs in children 5-15 years (based on the confidence interval of outcome 'percentage of total effect mediated'), because the evidence of 'indirect effect' is not significant, there cannot be a claim of an overall mediated effect. Because there were no mediated effects, the sensitivity analysis was not conducted.

Discussion

In this study, we aimed to explore how mediation analysis could be used to evaluate the impact of different health center mediators targeted by the PRIME intervention on malaria-related health outcomes of community children in Tororo, Uganda. In the

process, we learned several lessons concerning both the functioning of the intervention and the accommodations necessary to fit dynamic intervention processes into static statistical procedures. By reporting our experiences, we hope to inform others looking to apply mediation analysis to the evaluation of complex interventions.

Our findings identified that the intervention had an effect on two aspects of effective malaria case management: the availability of mRDTs to accurately diagnose fevers, and health workers' positive attitude towards their work including diagnosing and treating malaria and febrile illnesses. However, we found that these mediators did not lead to an improvement in community health outcomes. We have considered two possible interpretations. First, the mechanisms targeted by the intervention were on their own insufficient to lead to change. The intervention failed to address other possible mechanisms of effective malaria case management and as a result, the intervention effect could not be realized along the causal pathway. Second, the health centre outcomes were not large enough to lead to community level change. The small improvements made at the health centres appear to have been diluted by larger heath system shortfalls such as poor availability of health centre staff, infrastructure, and other health services (Chandler et al., 2017; Staedke et al., 2016). Similar interpretations were considered in the cluster RCT which found no difference in community health outcomes between the intervention and standard care study arms (Staedke et al., 2016). It is important to note that the results of this study provide an illustrative example of causal mediation analysis and should not be over-interpreted as the original PRIME trial was not powered for this extended analysis.

Our experience using causal mediation analysis revealed several challenges between the method and our approach to conceptualizing complex interventions. These challenges first arose when translating the intervention logic model and theory of change into an acyclical pathway of effect. This process was at odds with our conceptualization of how the intervention would work. DiLiberto et al. (2015) hypothesised that the intervention would work dynamically, igniting health workers' social and emotional processes to stimulate and sustain new skills and behaviours. This conceptualization was in line with approaches that define complex interventions as multidimensional and synergistic activities implemented into dynamic and unpredictable contexts (Cohn et al., 2013; Hawe, 2015). However, defining a linear configuration of variables reduced the complexity of the intervention and omitted the recursive and synergistic processes of how the intervention was hypothesised to work. The resulting causal pathways represented just two of many potential change processes. This simplification process highlights what others have noted as an incongruity between the precision required to define a model suitable for mediation analysis and the type of temporal and recursive change valued in evaluations of real world social and policy interventions (Aalen et al., 2012; Cartwright, 2007). This incongruity challenges the notion that mediation analysis can disentangle the complexity of an intervention's change processes into individual components ready to be refined, adapted, or discarded.

A second challenge was encountered when attempting to satisfy the method's assumption of independence of mediators – in other words, assuming there were no interactions between mediators along the causal pathway (Imai, Keele and Yamamoto, 2010). Interactions between multiple mediators can introduce unexpected sources of bias and confounding that cannot be easily accounted for with statistical manoeuvres (Imai and Yamamoto, 2013). To accommodate this requirement, we applied a single mediator model which assumed no relationship among the mediators and analysed each pathway separately. This model contrasted with the possibility that synergistic interactions between different components along the causal pathway were integral to how the intervention would work. We hypothesized that by establishing a community of practice at health centres and ensuring availability of AL and mRDTs, the intervention would produce multiple changes at the health worker and health centre level (mediators) which together would lead to improved health outcomes in the community. These multiple interactions are considered hallmarks of how complex interventions produce change and are encouraged in intervention design and evaluation (Cohn et al., 2013; Hawe, 2015). However, creating a single mediation model meant that these complex processes could not be included in the analysis. This simplified model not only yields conceptual challenges, it can also lead to biased estimates when the confounding effect of different mediators is not taken into account (Imai and Yamamoto, 2013). Approaches for multiple mediator analyses are developing but they remain a complex and technical endeavour (Daniel et al., 2015) and were beyond the scope of this study. The incompatibility between the contingent interactions of complex interventions and the

assumptions of independence necessary for mediation analysis challenges the notion that an analysis of multiple causal processes is achievable with this method.

A third challenge encountered was related to the assumption of no confounding along the pathway of effect between the intervention, mediators and outcomes. Unmeasured confounding can affect links between the mediator and the outcome and violate any claims to causality (Imai, Keele and Tingley, 2010). We observed many 'sources of confounding' in our study. In line with discussions of what contributes to the complexity of an intervention (Cohn et al., 2013; Hawe, 2015), the PRIME intervention was implemented in a 'crowded landscape' common in many low resource settings. In such landscapes, numerous government, non-governmental organizations (NGO) and research initiatives work in the same spaces to improve health services (Okwaro et al., 2015; Whyte et al., 2013). For example, some health centers in our study area received supplies of mRDTs from the government throughout the study period. This activity potentially confounded the causal pathway by decreasing stock-outs (mediator) and influencing health worker attitude and appropriate treatment of fever (outcomes) as health workers recognised the source of the mRDTs and modified their attitudes and uptake of mRDTs in response to who supplied them (DiLiberto, 2017). Likewise, some health centres and surrounding community areas were supported by NGOs, for example World Vision and Plan International, and received deworming medications and health centre equipment. This could have influenced health worker attitude (mediator) (constructs such as, 'This health center provides everything I need to do my job well') and population-level prevalence of anaemia (outcome) by decreasing worm infections,

an important contributor to childhood anaemia in the study area (Yeka et al., 2015). These types of activities occurred intermittently throughout the study period making it difficult to measure and include them as covariates in the analysis. Furthermore, these real-word events cannot be randomised and therefore cannot be assumed to have been evenly distributed between the intervention and standard care health centers. A sensitivity analysis could account for this confounding, however, Keele (2015) has shown that mediated effects are considered unreliable even with small violations of the assumption of no confounding. We believe that the complex real-world context of global health interventions would most likely lead to a violation of the assumption of no confounding calling into question the likelihood of producing reliable and interpretable results of mediated effects for studies implemented in dynamic contexts.

An extension of this third challenge of not being able to include contextual elements as possible confounders is also not recognizing them as having causal properties. As is the critique with RCTs more generally (Cohn et al., 2013; Hawe, 2015; Marchal et al., 2013), in mediation analysis context is bracketed out in order to produce causally interpretable results. As a result, it is not possible to develop more detailed understandings of the context in which the mechanisms under investigation in the analysis may or may not have produced outcomes. As suggested above, there were several contextual elements in our study that may have interacted with the intervention and/or the hypothesized mechanisms, or themselves have had an impact on the malaria-related health outcomes of community children. However, without a means of formally including these contextual elements in the analysis, their causal effects can

only be speculated, not evaluated. As an alternative methodology, realist evaluation provides an approach for formally including context in the analysis. The approach specifies what mechanisms will generate outcomes and what features of the context will affect whether or not those mechanisms operate (Pawson, 2013; Pawson and Tilley, 1997). When realist evaluations are conducted alongside RCTs, they foreground a multiplicity of contextual elements to make sense of the intervention change process and its plausibility for working in other contexts (Byng et al., 2005).

Our intervention was designed and evaluated at a time when the available guidance emphasized the use of randomized trials and accompanying methods that could be accommodated along the linear intervention input-outcome pathway (Craig et al., 2008; Moore et al., 2015). We were also informed by and aligned with emerging discussions that emphasized multidimensional views of complexity and context (Cohn et al., 2013; Hawe, 2015; Hawe et al., 2009; Mowles, 2014). We followed recommendations that appeared to accommodate these two logics and suggested the use of mediation analysis to combine data from outcome and process studies to produce a comprehensive evaluation of intervention change processes (Bonell et al., 2012; Moore et al., 2015). The aim of these comprehensive evaluations is to distinguish between intervention failure (the intervention was implemented adequately but failed to achieve its expected outcomes) and implementation failure (the intervention was implemented inadequately to achieve its outcomes) (Moore et al., 2015). We suggest the possibility of another type of failure – methodological failure which manifests as a mismatch between the logic of the intervention and context, and the logic of the methodology

resulting in a failure to appropriately evaluate the intervention processes and/or outcomes.

We have interpreted this mismatch to stem from different conceptualizations of complexity resulting in an epistemological incongruency that affected what was being analyzed and reported. Byrne and Callaghan (2014) have described two types of complexity – restricted and general. Restricted complexity uses mathematical approaches to explain how social reality experienced at the macro level is the result of interaction between elements at the micro level (i.e. relationships between variables in a mediation equation). It accommodates complexity by 'decomplexifying' or simplifying it into variables and their relationships. This conceptualization draws on a post-positivist epistemology where what can be observed and documented represents the truth about the social world. This conceptualization of complexity aligns with the logic of mediation analysis where the logic model, variables and assumptions of the method are considered to account for the complexity of the intervention and context. On the other hand, general complexity considers the iterative and unpredictable nature of human agency which requires explanations beyond the narrow rules and inferences of mathematical approaches. This requires an epistemological approach where reality is comprised of truths about the social world beyond what can be observed and documented. This aligns with our interpretation of the intervention and context as emergent and synergistic. Although there have been successful attempts at integrating different epistemological conceptualizations of phenomena to arrive at a more comprehensive understanding (Béhague et al., 2008; Behague and Goncalves, 2008)

we did not have this success. Instead, the epistemological incongruency between conceptualizations of complexity produced results about intervention that we could not reconcile with our experience of how it functioned in the real world.

The *epistemological and practical* challenges encountered in this analysis echo the assertion "that mediation effects are not simple by-products that can be produced for any intervention" (Keele, 2015: 511). However, mediation analysis may still have a role in analysing complex interventions. We suggest that *the method is best suited for studies adopting a conceptualization of restricted complexity which* should be *made* at the outset when designing the study *to support appropriate methodological choices and interpretation of results*. *Next, r*esearchers should decide their primary analytical objective as either analysis of intervention effect or analysis of mediation – with the recognition that these objectives require different study designs. While the objective of the RCT is to assess intervention effect, it is not an ideal design for assessing mediated effects. RCTs only randomize assignment to trial arms but not to mediators. These non-randomised mediators therefore remain subject to confounding (Imai, Keele and Yamamoto, 2010). A study design that prioritizes assessment of mediated effects would randomize assignment to the trial arm and to the mediator, and then compare these with the outcomes from a standard randomised design. These studies also need careful consideration to be adequately powered to investigate mediating mechanisms (Loeys et al., 2014; Schoemann et al., 2017). There are few applications of this type of study design, although there is growing interest for alternative designs and analyses within interventions research (Cousens et al., 2011; Lamont et al., 2016).

Additionally, researchers should decide if their intervention and theory of change can be designed to align with the acyclical logic necessary for statistical mediation analyses. A useful example is Angeles et al's (2014) approach to intervention design that defines different variables (independent, dependent, mediating, moderating, and control), postulates how these variables are related, and develops a logic model linking the variables in a series of if-then logic statements which is then validated. Their approach sets out a clear acyclical logic with a set of variables that are aligned with the those needed for mediation analysis. It is worthwhile to note, however, that these authors acknowledge the challenge with disentangling intervention components and highlight the importance of understanding how different intervention components interact with each other.

Finally, researchers could consider limiting their mediation analysis to assessing intervention effects on mediators only, and not extending the analyses to include outcome measures. This approach does not require the assumptions of mediation analysis to be satisfied and therefore produces a more realistic and interpretable assessment of mediation (Keele, 2015). A useful example is Abramsky et al's (2016) evaluation of the SASA! Intervention to reduce the occurrence of intimate partner violence against women in Uganda. This evaluation was limited to an assessment of the intervention on hypothesised community, partner, and individual-level mechanisms. The authors then inferred how mechanisms with significant effects might have influenced the intimate partner violence outcomes drawing on other studies to support

their theories. Importantly, and appropriately, the findings were interpreted as suggested mechanisms of effect rather than as evidence of a causal pathway.

Our experiences demonstrated several ways in which the logic of the intervention and context did not match the logic of mediation analysis which resulted in a simplification process that ultimately changed what was being analyzed and reported. The mismatch of logics is already understood in relation to the limitations of using the RCT to evaluate interventions conceptualized as contingent, system-wide change processes (Cohn et al., 2013; Hawe, 2015; Hawe et al., 2009). Indeed, the most recent update to the popular MRC guidance on designing and evaluating complex interventions recognizes these limitations and promotes a range of research perspectives, study designs and methods (Skivington et al., 2021). This is a welcomed update. However, as our conceptualizations of complexity diversify and sharpen, and the range of possible evaluation approaches proliferates, identifying the most appropriate methodologies becomes more challenging. We argue that sharing reflexive and transparent accounts of methodological challenges (and successes) will help others to avoid 'methodological failure' and support appropriate selection and application of methods that align with the conceptualization of complexity intervention logic and context. Sharing these 'behind the scenes' accounts can support assessments of internal validity, facilitate transferability of results, and inform future evaluations and interventions (DiLiberto et al., 2015; Reynolds et al., 2014). We have attempted to explain our methodological approach and the challenges we encountered, as well as provide suggestions to help others align mediation analysis with a conceptualization of restricted complexity and

evaluation goals, and to apply it more easily. With the promise of further updates to the guidance and resources available for the evaluation of complex interventions (Skivington et al., 2021), we argue that there should be a specific focus on 'methodologies in action' including careful consideration and transparent reporting of the methodological accommodations and decisions necessary to account for the different approaches to accounting for complexity that are inherent in how interventions and their contexts are conceptualized and evaluated.

List of abbreviations

AL - Artemether-Lumefantrine

MRC - Medical Research Council

mRDT - Rapid Diagnostic Test for Malaria

NGO - Non-Governmental Organization

RCT - Randomised Control Trial

Declarations

Ethics approval and consent to participate

The PRIME trial was approved by the Ugandan National Council for Science and Technology [details omitted for double-anonymized peer review], the Makerere University School of Medicine Research and Ethics Committee [details omitted for double-anonymized peer review], the London School of Hygiene and Tropical Medicine Ethics Committee [details omitted for double-anonymized peer review], and the University of California San Francisco Committee on Human Research [details omitted

for double-anonymized peer review]. The trial is registered at [details omitted for double-anonymized peer review]

The PROCESS Study was approved by Ugandan National Council for Science and Technology [details omitted for double-anonymized peer review], the Makerere University School of Medicine Research & Ethics Committee [details omitted for double-anonymized peer review], and the London School of Hygiene and Tropical Medicine Ethics Committee [details omitted for double-anonymized peer review].

Consent for publication

All PRIME Trial and PROCESS Study participants were informed of the purpose and nature of the study and consent was obtained before initiating participation in the study. which included consent for publication of anonymized data.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Tables and Figures

Table 1: Data sources and data collection procedures

	Measures used in mediation analysis
PRIME Trial (Staedke et al., 2013)	
Twenty public health centres (level II and III) in Tororo district were included; 10 randomised to the intervention and 10 to control. Clusters included households located within 2 km of health centres. The trial statistician generated the random allocation sequence and assigned clusters. Health centres were be stratified by level, and restricted randomisation was used to ensure balance on cluster location and size. Allocation was not blinded.	
Data collection procedures	
Cross-sectional survey: At baseline and annually for two years, community cross-sectional surveys were conducted with 8,766 children, including 4,383 under-five and 4,383 aged 5 to 15 years, to assess the impact of the intervention on prevalence of anaemia. The survey included a structured questionnaire administered to the primary caregiver, and a clinical and laboratory assessment of each participating child. Children were be sampled from each study cluster in proportion to the total cluster size, achieving a planned harmonic mean of 200 children per cluster. Using methods for a stratified, cluster-randomised design, and assuming a prevalence of anaemia of 65% at baseline, with a coefficient of variation (k) between clusters of 0.2, this sample size allowed us to detect an absolute difference in anaemia prevalence between study arms of 17% (or more) with 80% power at a 5% significance level.	Prevalence of anaemia in children under five and 5-15 years
Patient exit interviews: At baseline and annually for two years, exit interviews were conducted with caregivers of children under five at all health centres to assess the impact of the intervention on appropriate treatment of fever. Caregivers were interviewed using a standardised questionnaire to gather information about the purpose of their visit, diagnosis given, and medications prescribed and received. A clinical evaluation of the child was also performed by a study physician. Patients were selected by convenience sampling from each facility to participate in the interviews. In the first two rounds, 10 patients were recruited from each facility to participate (200 total); in the final survey, 50 patients were recruited to participate (1,000 total); 1,400 patients total across 3 rounds. In the final survey, assuming the proportion of children inappropriately treated was 35% in the standard care arm, with k= 0.2, interviewing 1000 patients allowed us to detect an absolute difference of 12% (or more) with 80% power at a 5% significance level.	Appropriate treatment of fever
Health centre surveillance: Surveillance activities were conducted at all health centres initially every month, to collect information about patient attendance, drug stocks, staffing, and health centre costs. After the first year, data were collected every two to three months. Data were collected using a modified version of the outpatient department register and the drug and mRDT stock cards. AL is packaged in 4 dosing sizes depending on the patient's age and weight.	Health centre stocks of AL and mRDTs
PROCESS Study (Chandler et al., 2013)	
A mixed-methods evaluation conducted alongside the PRIME Trial designed to further our understanding about why the PRIME intervention was effective, or not. The study included an evaluation of the implementation of the intervention activities; mechanisms of change from the perspective of implementers, health workers, community members, and key stakeholders; a context evaluation to capture information on factors that may affect the implementation of the intervention or outcomes; and an assessment of the wider impact of the intervention beyond outcomes of the PRIME trial.	
Data collection procedures	
Patient exit interviews: At baseline, immediately after the intervention implementation, and between 9 and 12 months after the intervention, patient exit interviews were conducted with caregivers of children under five in both trial arms to assess caregiver satisfaction with the consultation, specifically with the	Patient satisfaction

interpersonal skills of the health worker. Caregivers were interviewed using a structured questionnaire adapted from an existing questionnaire developed in Canada (Stewart et al., 2004). Patients were selected by convenience sampling from each facility to participate in the interviews. In each health centre 5 interviews were conducted in each round (100 total) for 300 interviews total.	
Health worker questionnaires: Between 9 and 12 months after the intervention started, health worker questionnaires were conducted to assess motivation and feelings towards work including both 'internal motivation' and 'external motivation'. The questionnaires was adapted from a tool piloted in Tanzania (Chandler et al., 2009) and was designed for self-completion by all health workers in both arms of the trial and included a series of responses to statements with four-point Likert scale response options, from 'strongly agree' to 'strongly disagree'. Open-ended questions were also included on each topic to encourage expansion by respondents.	Health worker attitude

Table 2: PRIME intervention pathways for mediation analysis

Exposure	Mediator			Outcome		
	Measure	Measured at	Applies to age group	**Measure**	Measured at	For age group
Pathway 1: Effect of intervention on mechanisms mediated by AL and mRDT stocks						
Trial arm: PRIME Intervention or Standard care	**Stocks of AL**	12 months preceding midline survey	Under 5 & 5-15 years	**Health worker attitude**	Midline survey	Under 5 & 5-15 years
				Patient satisfaction	Midline survey	Under 5 years
				Appropriate treatment of fever	Midline survey	Under 5 years
	Stocks of mRDTs	12 months preceding midline survey	Under 5 & 5-15 years	**Health worker attitude**	Midline survey	Under 5 & 5-15 years
				Patient satisfaction	Midline survey	Under 5 years
				Appropriate treatment of fever	Midline survey	Under 5 years
Pathway 2: Effect of intervention on community health outcomes mediated by mechanisms						
Trial arm: PRIME Intervention or Standard care	**Health worker attitude**	Midline survey	Under 5 & 5-15 years	**Proportion anaemic**	Final survey	Under 5 & 5-15 years
	Patient satisfaction	Midline survey	Under 5 years	**Proportion anaemic**	Final survey	Under 5 years
	Appropriate treatment of fever	Midline survey	Under 5 years	**Proportion anaemic**	Final survey	Under 5 years
	Stocks of AL	12 months preceding midline survey	Under 5 & 5-15 years	**Proportion anaemic**	Midline survey	Under 5 & 5-15 years
		24 months preceding final survey	Under 5 & 5-15 years	**Proportion anaemic**	Final survey	Under 5 & 5-15 years
	Stocks of mRDTs	12 months preceding midline survey	Under 5 & 5-15 years	**Proportion anaemic**	Midline survey	Under 5 & 5-15 years
		24 months preceding final survey	Under 5 & 5-15 years	**Proportion anaemic**	Final survey	Under 5 & 5-15 years

Table 3: Health centre, health worker and patient characteristics

Health centre	Average monthly patient load	Total number of health workers
Standard care		
1	183.18	1
2	178.18	2
4	243.47	5
5	164.71	2
7	249.65	6
12	186.88	2
14	162.71	2
16	225.47	2
17	128.94	2
19	124.47	3
Overall	193.77	2.7
Intervention		
20	144.24	2
3	230.47	1
18	279.82	5
15	183.59	2
13	144.41	2
8	160.41	1
9	216.00	6
10	193.76	2
11	236.88	3
6	232.24	2
Overall	202.18	2.6

Table 4: Mediator and outcome measures by health centre

	Mediator measure							Outcome measure			
Health centre	Health worker attitude score	Patient satisfaction score	Appropriate treatment score	Months stock-out of AL, Baseline to midline survey	Months stock-out of mRDTs, Baseline to midline survey	Months stock-out of AL, Baseline to final survey	Months stock-out of mRDTs, Baseline to final survey	Proportion anaemic, Under 5, Midline	Proportion anaemic, 5-15 yrs, Midline	Proportion anaemic, Under 5, Final survey	Proportion anaemic, 5-15 yrs, Final survey
Standard care											
1	55%	87%	77%	8.87	14.8	8.03	12.27	54.4%	23.4%	76.2%	54.8%
2	39%	74%	74%	15.37	26.77	0	1.33	66.8%	34.1%	73.6%	35.2%
4	40%	84%	71%	6.5	10.47	6.77	8.1	56.7%	31.2%	63.3%	31.2%
5	47%	74%	70%	8.1	21.07	0	1.1	50.2%	17.4%	63.9%	27.3%
7	50%	82%	67%	5.93	15.33	0	1.57	46.3%	12.3%	63.9%	22.9%
12	49%	94%	44%	4.83	14.63	0.97	3.73	61.0%	24.6%	64.0%	25.9%
14	48%	74%	71%	12.93	22.83	8	11.23	53.6%	27.2%	57.5%	27.6%
16	39%	88%	71%	5.3	18.8	7.43	11.9	77.4%	38.5%	52.9%	25.8%
17	41%	79%	88%	4.93	11.43	8.4	13.17	45.3%	19.8%	52.8%	24.5%
19	44%	82%	85%	11.23	29.47	8.23	11.7	63.3%	32.5%	66.7%	32.1%
Overall	45%	82%	72%	8.4	18.56	4.78	7.61	58.0%	26.4%	64.2%	31.4%
Intervention											
20	52%	80%	50%	12.83	23.43	0.03	0.3	43.0%	10.8%	45.2%	25.8%
3	37%	80%	77%	10.63	22.17	0.2	0.37	59.5%	18.8%	62.3%	26.7%
18	50%	87%	87%	5.83	17.5	0.7	1.23	44.7%	17.6%	56.1%	24.3%
15	54%	89%	64%	5.87	16.97	0.6	2.67	44.1%	23.4%	61.8%	28.0%
13	55%	76%	78%	8.87	19.83	1	1	50.0%	14.9%	67.9%	29.8%
8	54%	81%	68%	5.7	14.93	0.73	2.33	60.9%	16.7%	66.7%	25.4%
9	61%	83%	74%	10.87	20.5	2.1	2.3	59.4%	23.3%	65.3%	45.3%
10	53%	80%	90%	5.9	18.37	0.37	0.97	44.5%	15.6%	69.8%	37.5%
11	46%	88%	77%	5.87	9.13	1	2.33	51.0%	15.4%	65.1%	37.7%
6	42%	89%	87%	5.27	11.7	0	0.5	54.1%	31.2%	69.7%	25.1%
Overall	50%	83%	75%	7.76	17.45	0.67	1.4	52.4%	19.3%	64.2%	30.8%

Table 5: Effect of the intervention on mediator measures

			Crude	Adjusted
Mediator measure		Mean (SD)	Regression coefficient (95% CI)	Regression coefficient (95% CI)
Health worker attitude	Control	0.45 (0.05)	1	1
	Intervention	0.5 (0.07)	0.05 (-0.01, 0.11)	0.06 (-0.01, 0.12)
Patient satisfaction	Control	0.82 (0.07)	1	1
	Intervention	0.83 (0.05)	0.01 (-0.04, 0.07)	0.02 (-0.03, 0.08)
Appropriate treatment of fever	Control	0.72 (0.12)	1	1
	Intervention	0.75 (0.12)	0.03 (-0.08, 0.15)	0.04 (-0.08, 0.16)
Stock-outs of AL, baseline to midline survey	Control	9.2 (4.51)	1	1
	Intervention	8.91 (3.43)	-1.11 (-6.3, 4.09)	-1.24 (-6.56, 4.08)
Stocks-outs of RDTs, baseline to midline survey	Control	5.46 (4.22)	1	1
	Intervention	0.75 (0.65)	-6.21 (-9.66, -2.76)	-5.96 (-9.66, -2.26)
Stock-outs of AL, baseline to final survey	Control	18.56 (6.39)	1	1
	Intervention	17.45 (4.51)	-0.29 (-4.05, 3.48)	-0.36 (-4.28, 3.57)
Stocks-outs of RDTs , baseline to final survey	Control	7.61 (5.1)	1	1
	Intervention	1.4 (0.92)	-4.7 (-7.54, -1.86)	-4.46 (-7.46, -1.46)

Table 6: Pathway 1 – Mediated effects of the intervention on intermediate outcomes

		Regression coefficient (95% CI)
Effect of the intervention on intermediate outcomes mediated by stocks of AL		
Intervention → HW attitude mediated by Stocks of AL	Indirect effect	0.01 (-0.01, 0.01)
	Direct effect	0.05 (0, 0.11)
	Total effect	0.05 (0, 0.11)
	% of total effect mediated	0.01 (-0.01, 0.01)
Intervention → Patient satisfaction mediated by Stocks of AL	Indirect effect	0.01 (-0.03, 0.03)
	Direct effect	0.01 (-0.03, 0.06)
	Total effect	0.01 (-0.04, 0.07)
	% of total effect mediated	0.04 (-0.95, 0.59)
Intervention → Appropriate treatment of fever mediated by Stocks of AL	Indirect effect	0.01 (-0.03, 0.03)
	Direct effect	0.04 (-0.07, 0.15)
	Total effect	0.04 (-0.07, 0.14)
	% of total effect mediated	0 (-0.04, 0.03)
Effect of the intervention on intermediate outcomes mediated by stocks of mRDTs		
Intervention → HW attitude mediated by Stocks of mRDTs	Indirect effect	0.01 (-0.05, 0.04)
	Direct effect	0.06 (-0.01, 0.13)
	Total effect	0.05 (0, 0.11)
	% of total effect mediated	-0.07 (-0.5, 0.16)
Intervention → Patient satisfaction mediated by Stocks of mRDTs	Indirect effect	-0.01 (-0.06, 0.02)
	Direct effect	0.03 (-0.03, 0.1)
	Total effect	0.01 (-0.04, 0.06)
	% of total effect mediated	-0.42 (-8.28, 9.58)
Intervention → Appropriate treatment of fever mediated by Stocks of mRDTs	Indirect effect	-0.06 (-0.17, 0.02)
	Direct effect	0.1 (-0.03, 0.24)
	Total effect	0.04 (-0.08, 0.14)
	% of total effect mediated	-0.87 (-14.93, 12.74)

Table 7: Pathway 2 – Mediated effect of the intervention on community health outcomes

		Under 5	5-15 years
		Regression coefficient (95% CI)	Regression coefficient (95% CI)
Mediated effect of the intervention on anaemia prevalence at the midline community survey			
Intervention → Anaemia mediated by Stocks of AL	Indirect effect	0 (-0.03, 0.02)	-0.01 (-0.04, 0.03)
	Direct effect	-0.06 (-0.13, 0.02)	-0.07 (-0.12, -0.01)
	Total effect	-0.06 (-0.14, 0.01)	-0.07 (-0.14, -0.01)
	% of total effect mediated	0.05 (-0.22, 0.44)	0.08 (0.04, 0.37)
Intervention → Anaemia mediated by Stocks of mRDTs	Indirect effect	-0.01 (-0.07, 0.05)	-0.03 (-0.09, 0.01)
	Direct effect	-0.05 (-0.15, 0.05)	-0.04 (-0.11, 0.04)
	Total effect	-0.06 (-0.14, 0.01)	-0.07 (-0.14, -0.01)
	% of total effect mediated	0.12 (-0.86, 1.2)	0.46 (0.22, 2.22)
Mediated effect of the intervention on anaemia prevalence at the final community survey			
Intervention → Anaemia mediated by Health worker attitude	Indirect effect	0.03 (0 , 0.08)	0.01 (-0.02, 0.06)
	Direct effect	-0.03 (-0.1, 0.04)	-0.01 (-0.09, 0.07)
	Total effect	0 (-0.07, 0.06)	0 (-0.07, 0.07)
	% of total effect mediated	-0.43 (-11.39, 12.68)	-0.19 (-6.32, 3.4)
Intervention → Anaemia mediated by Patient satisfaction	Indirect effect	0 (-0.03, 0.02)	--
	Direct effect	0 (-0.07, 0.07)	--
	Total effect	0 (-0.07, 0.07)	--
	% of total effect mediated	0.07 (-1.83, 1.32)	--
Intervention → Anaemia mediated by Appropriate treatment of fever	Indirect effect	0 (-0.03, 0.02)	--
	Direct effect	0 (-0.07, 0.07)	--
	Total effect	0 (-0.07, 0.07)	--
	% of total effect mediated	0.06 (-1.46, 1.23)	--
Intervention → Anaemia mediated by Stocks of AL	Indirect effect	-0.01 (-0.04, 0.03)	0 (-0.02, 0.02)
	Direct effect	0 (-0.06, 0.07)	0 (-0.07, 0.08)
	Total effect	0 (-0.07, 0.06)	0 (-0.08, 0.07)
	% of total effect mediated	0.09 (-2.07, 2.59)	-0.02 (-0.74, 0.57)
Intervention → Anaemia mediated by Stocks of mRDTs	Indirect effect	0.03 (-0.03, 0.09)	-0.03 (-0.1, 0.03)
	Direct effect	-0.03 (-0.12, 0.06)	0.03 (-0.07, 0.13)
	Total effect	0 (-0.08, 0.06)	0 (-0.08, 0.07)
	% of total effect mediated	-0.41 (-13.99, 17.86)	-0.24 (-11.5, 16.38)