Emulating value-chains of fast-moving consumer goods to improve uptake of co-packaged ORS and zinc for childhood diarrhoea: evaluation of the ColaLife trial

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ABSTRACT

Introduction Oral rehydration salts (ORS) and zinc comprise the globally recommended treatment for diarrhoea in children aged <5 years. However, limited access contributes to low uptake of this treatment and subsequently high rates of morbidity and mortality among this age group in low-income and middle-income countries. We adopted approaches used for private-sector value-chains of fast-moving consumer-goods, involving the simultaneous stimulation of supply and demand. These approaches were applied to the introduction of an innovative co-packaged diarrhoea-treatment kit (ORSZ co-pack) to increase ORS and zinc coverage at the community level in Zambia.

Methods We tested our approach using an observational pre–post test study design in two intervention districts in rural Zambia (Kalomo and Katete), each with a matched comparator (Monze and Petauke, respectively). We assessed the effect on coverage, of ORS and zinc as well as ORS alone, by conducting household surveys of a total of 2458 and 2477 caregivers of children aged <5 years at baseline and endline, respectively, across the four districts. We also assessed whether the source of ORS (public or private sector) changed following the intervention.

Results Both intervention districts experienced significant increases in coverage of ORS and zinc from <1% at baseline to 46.9% and 46.3% in Kalomo and Katete, respectively. Uptake in the comparator districts remained low at 1.7% and 0.6% in Monze and Petauke, respectively. For the secondary outcome examining ORS coverage (with or without zinc), the intervention was associated with a significant increase in Kalomo versus Monze, but not in Katete versus Petauke. There was a clear shift from the public to the private sector, and specifically to the use of the ORSZ co-pack.

Conclusion Implementation of a value-chain creation approach for an innovative, over-the-
Processes and systems

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

Implementation of a private-sector-inspired, value-chain creation approach for the distribution of co-packaged ORS and zinc can significantly improve the coverage of this globally recommended treatment at the community level in LMICs.

counter, co-packaged diarrhoea-treatment kit can significantly improve the coverage of ORS and zinc.

INTRODUCTION

While deaths from childhood diarrhoea have declined over recent decades, the disease remains a leading cause of avoidable morbidity and mortality in children aged less than 5 years.1–4 Globally, diarrhoea is the fourth-leading overall cause and second-leading infectious cause of child deaths, after preterm birth complications, lower respiratory infections and intrapartum-related events, accounting for approximately 9.1% (ie, 0.48 million) of childhood mortality.5–7 A similar trend is seen in Zambia, with diarrhoea accounting for approximately 9% of childhood mortality.8–9 Globally and in Zambia, rotavirus is a leading cause of diarrhoea in children.8–9 It is widely accepted that the use of oral rehydration salts (ORS) with 10–14 days of zinc supplementation (ORS and zinc) can reduce childhood deaths from diarrhoea.10–12 This combination therapy is safe and effective for use in both home and healthcare-facility settings when properly prepared and administered. The therapy has various other beneficial attributes, including being off-patent, cheap, and relatively easy to manufacture locally and distribute when compared with other pharmaceutical products.13 Together, ORS and zinc form the primary treatment recommendation from the WHO and UNICEF for diarrhoeal diseases in children.14 15 ORS can significantly reduce diarrhoea-related deaths, while zinc supplementation can reduce the duration, severity and recurrence of diarrhoeal diseases in children in the 2–3 months following its use. Despite this, coverage (defined as the share of the population with need utilising a defined set of healthcare goods and services; also referred to in this paper as uptake) of the combination therapy of these two products remains very low globally.

Treatment access

In Zambia, as in many low-income and middle-income countries (LMICs), both ORS and zinc can be purchased over the counter, usually as separate products. However, globally recognised barriers to access exist, relating to both supply and demand; these barriers include insufficient production, distribution, promotion and awareness.16 One systematic review found that, while copromotion of ORS and zinc can improve the level of ORS use, few high-quality studies have investigated the effectiveness of interventions to promote the use of this combined therapy.17 Globally, it is estimated that less than 7% of children with acute diarrhoea receive zinc, and only around 42% of them are given ORS.18 In Zambia, estimations made prior to our intervention showed that zinc coverage was <1%, while coverage of sachet-based ORS was 64%.19 Rural areas in Zambia, as in many LMICs, tend to have the greatest burden of diarrhoea, yet access to ORS and zinc is particularly problematic in these areas, with public sector supply unreliable and private sector availability limited, particularly for zinc.20–26

Social innovation for the treatment of childhood diarrhoea: a value-chain approach

To address this situation, we adopted a multipronged approach involving the development of an improved and innovative co-packaged ORS and zinc product, together with the creation of its end-to-end value-chain. The improved ORS and zinc product was designed with consideration of what the end-user wants (rather than what they are perceived to need) at the forefront of the design process. This was the foundation of creating an end-to-end value-chain,27 a business model that is broader than the supply chain model, as it also takes account of product design, research and development, marketing, profit margins, delivery and use, that is, it conceptualises the transformation of a product or service from concept to community.28

The primary focus of value-chains is on the benefits that accrue to end-users, with value generated when the needs (and, more importantly, the desires) of these end-users are met through the provision of products or services.29 When customers at the end of a value-chain perceive a product as having value, this creates a ‘demand pull’ on the product, facilitated by intermediaries (ie, wholesalers and community-level, private-sector retailers) who can make a profit while fulfilling demand, as value flows back down the value-chain (figure 1). This differs from traditional public sector supply-chain management, which begins with an agency (eg, ministry of health) who ‘pushes’ product out.30 Value-chain principles have generally been applied to commercial, fast-moving consumer-goods (FMCGs), such as beverages (eg, Coca-Cola), toiletries and groceries. These principles have not typically been combined to improve access to essential public health products.

The provision of ORS and zinc via public sector clinics alone has proved an ineffective strategy;10 incorporating the private sector to strengthen supply chains and learning from commercial approaches has been advocated as a promising way to reach the wider population.16 20 Since 2009, UNICEF and WHO have been proposing the co-packaging of ORS and zinc as a means of increasing coverage of ORS and zinc.11 Thus, the aim of this study was to test the hypothesis that uptake of ORS and zinc combination therapy for childhood diarrhoea can be significantly increased in rural communities by simultaneously creating an innovative
co-packaged ORS and zinc product together with its value-chain. In other words, creating a desirable ORS and zinc (ORSZ) co-pack, generating a demand for it through marketing, and making it profitable for all those involved in fulfilling that demand: distributors, wholesalers and community-level rural retailers.

METHODS
Patient and public involvement: creating the value-chain
To create the value-chain, focus groups involving caregivers of children under-5 living in rural Zambia were used to gain a better understanding of end-user challenges, desires and willingness-to-pay, with respect to treating diarrhoea in the home. Consultations with retailers, wholesalers, and manufacturers were also used to help determine the typical margins expected by each. These were then used to inform the design of the intervention and calculate a target ex-factory price for the ORSZ co-pack.

To meet this target ex-factory price in the trial phase, a subsidy was applied at the top of the value-chain (ie, the manufacturer’s end), with a view to subsequently eliminating this subsidy during the scale-up phase through economies of scale and other efficiencies, such as product design modifications indicated by the trial. The benefits of subsidising the top of the value-chain in this way were twofold. First, it enabled creation and testing of the value-chain, which is required to achieve the demand-pull effect, during the trial phase. Second, a subsidy at the manufacturer level is visible only to that actor; therefore, to eliminate the subsidy during the scale-up, post-trial, involves only the manufacturer and does not affect other actors’ expectations in the newly established value-chain. This enabled eventual scale-up to proceed using the value-chain established and tested during the trial.

Intervention: market shaping, Kit Yamoyo and demand generation
Market shaping
Market shaping for health products helps to optimise price, quality, design, and sustainable supply towards maximisation of public health impact. Typically, this involves ensuring continued availability and affordability of high-quality health products; accelerating the adoption of new, more cost-effective products; preparing for country adoption and long-term market viability; and strengthening key foundational elements, such as regulatory policies. In this way, market-shaping interventions act on different aspects and stages of a product’s value-chain. In this case, market shaping included: (1) understanding customer needs and demands to support the design and development of an innovative, desirable and affordable co-packaged ORS and zinc product; (2) establishing the steps in an end-to-end value-chain based on existing channels for FMCGs such as soft drinks; (3) establishing price points by working backwards from the target retail price of 5 Zambian Kwacha (ZMW) (~US$0.93), based on typical margins for FMCGs: 19% at wholesale level and 35% at retail level and (4) demand-generation activities at the community level.

With regard to the cost to the consumer, while government clinics may offer medicines free of charge, caregivers often face other costs associated with traveling to distant clinics. Real costs may include travel and subsistence; opportunity costs include taking time off work and the risks associated with treatment delay. One rural Zambian study found that distance was a significant predictor of attendance for diarrhoea treatment specifically. In addition to geographical access barriers, public sector facilities face regular stock outs of essential medicines like ORS and zinc. Thus, despite basic medicines being made available free of charge to patients as of 2006 in Zambia, essential and life-saving drugs were still widely unavailable in health facilities. We postulated that a reduction in distance travelled would decrease opportunity costs, thus offering caregivers the option to pay an affordable price in the private sector. Furthermore, and specific to co-packaged ORS and zinc, it should be noted that in the market, evidence from numerous countries suggests that co-packs may be cheaper than ORS and zinc bought separately.

Co-packaged ORS and zinc product: Kit Yamoyo
Branded as Kit Yamoyo (meaning ‘kit of life’ in various local languages), the co-packaged ORS and zinc product designed for the ColaLife trial included several innovative features, informed by a human-centred design process implemented through focus-group work with end-users and community-level retailers. These features were then incorporated in the final product design in close collaboration with a local pharmaceutical manufacturer in Lusaka and a UK-based packaging design company. Our manufacturing partner showed a willingness to share the risk of developing a new ORSZ co-pack based on access to research findings and key design insights, total ownership of the intellectual property, shared initial production costs and a process focused on codevelopment. The resulting product served as the foundation...
for the value-chain and exhibited the following unique features.

First, the product contained eight small sachets of low-osmolarity ORS, with each 4.12 g sachet formulated to make 200 mL of solution. Normally, health centres provide one or two larger sachets of ORS, with each sachet containing sufficient ORS to make 1 L of solution, most of which would be wasted as it is more than a child aged <5 years typically consumes in 1 day. Moreover, ORS solution should be discarded within 24 hours of preparation to avoid contamination, so multiple, smaller sachets are more appropriate for home-based treatment over several days.

Second, the co-packaging of ORS with zinc has previously been demonstrated to be an effective way to market and encourage the combined use of these products. Given the low coverage of zinc, a blister pack containing ten zinc sulphate tablets was co-packaged with the ORS, along with pictographic instructions for preparing the ORS solution and to indicate the correct dosage of zinc. A small bar of hand soap was also included in the co-pack during the pilot, to reinforce the message of personal hygiene and prevention, and also to make the kit more attractive.

Finally, our human-centred design process demonstrated that most caregivers had no means of accurately measuring the appropriate volume of water required to mix the ORS, so the product packaging, which housed all of the contents of the kit, was designed to act as a measuring device to facilitate proper preparation, mixing and drinking of the ORS solution. The product container was marked to indicate the 200 mL of water required to prepare the ORS solution at the correct concentration. This container was also designed to fit in the empty spaces between the necks of crated bottles of Coca-Cola, to facilitate transport by private retailers, the providers of the co-pack at the community level (figure 2).

**Demand generation**

For demand generation, approximately 30 existing community health workers (CHWs) in each of the two intervention districts were trained in the product-specific and general benefits of ORS and zinc, reinforcing their prior knowledge around definitions, appropriate treatment-seeking behaviour, signs and stages of dehydration, indications for referral, hand washing and other preventive behaviours. Ninety-six retailers (ie, 50 and 46 village shops in Kalomo and Katete, respectively) were similarly trained (training resources used are available here). CHWs promoted and demonstrated the ORSZ co-pack at community health centres and during outreach activities, distributed vouchers and referred customers to participating shops. Outreach activities included community events, plays, radio spots and caregiver testimonials. Retailers were provided with posters and encouraged to promote the ORSZ co-pack.

Project-trained wholesalers purchased ORSZ co-packs directly from the manufacturer. Orders were delivered by Medical Stores, the parastatal responsible for distributing public-sector drugs to the district level in Zambia. Retailers followed their usual patterns for FMCGs, purchasing kits from wholesalers located in district centres and transporting them to their shops, via their usual mode of transport (bicycle, public transport, eg, minibus). These shops were the point-of-sale to caregivers. The recommended retail price, based on willingness-to-pay studies, was ZMW5.00 (~$0.93). Price points along the value-chain were recommended, not controlled.

In a reversal of conventional ‘cost-plus-pricing’, we deployed a ‘price-minus-costing’ (ie, target costing) approach. This involved determining the price points along the value-chain from the willingness-to-pay retail price and the margins expected by wholesalers and retailers. Using this approach, it was necessary to subsidise the ex-factory price (by 60%), to ensure that wholesalers and retailers made acceptable margins and that the product remained affordable to the majority of caregivers at the end of the value-chain. Economies of scale achieved during scale-up have subsequently removed the need for a subsidy.

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**Figure 2** The Kit Yamoyo anti-diarrhoea kit: co-packaged ORS and zinc, soap, and information leaflet. IEC, information, education, communication; ORS, oral rehydration salts.
Use of vouchers
To generate the ‘pull’ required for private-sector distribution systems to work, strong demand for the product is required on the part of the customer, in this case caregivers. Such demand would normally be built up over several years and might involve promotions, such as discount vouchers, to encourage first-time use. Vouchers are an end of value-chain subsidy; such a subsidy increases demand and strengthens the value-chain without affecting the price points or processes within it.

Vouchers were deployed during the first 6 months of this study. These were given to caregivers during CHW demonstrations of the product to help kick-start demand. However, throughout the study, including during the first 6 months, caregivers also bought the kits using cash. Wholesalers and retailers bought and paid for the product in the usual way, in response to the demand for the kits.

The value of the vouchers was set at the level of the willingness-to-pay established during the pretrial, caregiver focus groups. During the first 6 months of the trial phase, CHWs activated 23 982 vouchers; of these, 10 415 were redeemed. Retailers could redeem vouchers using their mobile phone or by visiting the district project office. Over the 12 months of the trial, retailers bought 26 735 kits to sell in their communities and redeemed 10 415 vouchers, giving a ratio of cash sales to voucher sales of 61:39.

Study design
A 9-month consultation phase, which ranged from human-centred product design involving caregivers in rural Zambia, to establishing a steering committee made up of public and private stakeholders involved in diarrhoea control (chaired by the Ministry of Health), to developing a thorough understanding of the regulatory environment in Zambia for public health products, resulted in the development of an innovative, locally manufactured ORSZ co-pack45 and its mapped-out value-chain. A subsequent 12-month pilot study focused on the creation and activation of the value-chain, including continued market-shaping, using existing private-sector channels to facilitate availability of the ORSZ co-pack in two purposively selected, remote, rural intervention districts: Kalomo and Katete (figure 3).

Selection of districts
Selection criteria for the intervention districts included rurality (but within 1 day’s drive of Lusaka to enable effective trial management), mobile phone coverage (to support the extension-based retailer support system), high diarrhoea rates and an independent, general wholesaler interested in participating. Introductions to these were facilitated through The Coca-Cola Company’s local bottling partner, SABMiller, through an advisory, non-financial public-private partnership established for the purpose of this study.

The ORSZ co-pack was made available through independent, private sector, general retail shops located at the community level throughout the intervention districts. Using a quasi-experimental pre–post test design, each intervention district (ie, Kalomo and Katete) in this observational study was matched with a comparator district (Monze and Petauke, respectively), giving two sets of intervention and comparator arms. Comparators were selected from the same province, sharing similarities with regard to rurality, livelihoods (predominantly agrarian), language/tribe, road intensity, diarrhoea burden in children aged <5 years, education levels, age distribution of caregivers, and ORS and zinc coverage levels (table 1); and following substantial consultation with local partners who deemed the selected comparators to be most similar to the intervention districts. No intervention was made in comparator districts, which continued to have access to diarrhoea treatment almost exclusively through public-sector rural health centres. Historically, the retail pharmacy network in Zambia is poorly developed, with just 59 retail pharmacies country-wide, concentrated in urban centres, all but 19 in the capital, Lusaka.46 Access to ORS or zinc through the private sector was very limited in rural parts of the country. Where treatments were available in the private sector, these were typically limited to 1 L ORS sachets. There was no evidence of zinc (alone) or co-packaged ORS and zinc products being available on the market.

Outcomes
The primary outcome was coverage of ORS and zinc, defined as the proportion of children aged <5 years with diarrhoea in the previous 2 weeks who received ORS with zinc. Diarrhoea was defined as three or more
loose or watery stools within a 24-hour period. Baseline figures for zinc use were <1%, so we compared the difference in coverage proportions between each intervention and comparator arm at the endline only. In line with global reporting standards, the use of ORS and zinc was based on a caregiver reporting that a child with diarrhoea had received both medicines. The primary outcome was measured in a representative, repeated, cross-sectional survey (ie, different households at baseline and 1 year later at endline, following implementation of the trial). We also examined the difference in total ORS coverage (ie, with or without zinc) between intervention and comparator districts at baseline and endline. In addition, we assessed the shift from public-sector access of recommended treatment to private-sector access.

Study population and sample size

We conducted household surveys with primary caregivers (mainly mothers) of children aged <5 years at baseline (August 2012, n=2458) and endline (August 2013, n=2477). Rural sampling sites (12–15 sites per district) were defined by the presence of a community retailer (or a cluster of retailers) at the centre of the site. Each site served as an enumeration area and had a 5 km radius, covering an area of 78.6 km². The centre of each site was at least 10 km from a town. Retailers were identified in collaboration with the district’s municipal government during a prestudy survey that attempted to identify all rural retailers in the district.

Households were selected using a modified random-walk technique with probability proportional to population size (PPS) within each site. Population size per site was determined based on data provided by Zambia’s Central Statistics Office. The first household to be sampled was randomly selected along the site perimeter; subsequently, every third household was sampled to reduce clustering effects. In multi-family households with more than one eligible caregiver, only one caregiver was selected for inclusion, and only primary caregivers aged 16 years or more were included. To eliminate intrahousehold correlation, only one child per household was selected. In cases where there were multiple children aged <5 years, caregivers were asked to base their responses on a child who had experienced diarrhoea within the 2 weeks preceding the survey. If multiple children aged <5 years had experienced diarrhoea, the reference child was selected alphabetically. This was accounted for during analysis to avoid introducing bias in the calculation of diarrhoea prevalence.

Table 1

Characteristics of the intervention (Kalomo and Katete) and comparator districts (Monze and Petauke, respectively) at baseline, 2012

| Characteristic                                      | Southern province | Eastern province |
|-----------------------------------------------------|-------------------|------------------|
|                                                    | Kalomo (intervention) | Monze (comparator) | Katete (intervention) | P value* | Petauke (comparator) | P value* |
| Mean age of respondent caregiver                   | 30 (SD: 10.1) n=619 | 30 (SD: 9.9) n=610 | 29 (SD: 8.2) n=611 | 0.439 | 29 (SD: 8.8) n=587 | 0.569 |
| Caregiver has above primary education (%)           | 12.9 (SD: 33.6) n=619 | 14.5 (SD: 35.2) n=608 | 4.0 (SD: 19.7) n=622 | 0.540 | 4.8 (SD: 21.5) n=600 | 0.421 |
| Caregivers who cited diarrhoea as a main health issue of children aged <5 years in their community (%) | 79.1 (SD: 40.7) n=620 | 82.0 (SD: 38.5) n=611 | 81.3 (SD: 39.0) n=623 | 0.368 | 79.5 (SD: 40.4) n=604 | 0.487 |
| Caregivers who cited they typically accessed the public sector for ORS (%) | 99.4 (SD: 9.3) n=456 | 99.7 (SD: 4.6) n=471 | 99.4 (SD: 7.6) n=514 | 0.207 | 99.5 (SD: 6.5) n=469 | 0.884 |
| Proportion of households with diarrhoea in children aged <5 years in the previous 2 weeks (%) | 37.1 (SD: 48.3) n=620 | 31.5 (SD: 46.6) n=611 | 39.3 (SD: 48.9) n=623 | 0.189 | 43.2 (SD: 49.6) n=604 | 0.100 |
| Proportion of children aged <5 years with diarrhoea who used ORS plus zinc (%) | 0.4 (SD: 6.6) n=230 | 0 (SD: 19.4) n=194 | 0.4 (SD: 6.4) n=245 | 0.358 | 0 n=261 | 0.302 |
| Proportion of children aged <5 years with diarrhoea who used ORS (with or without zinc) (%) | 48.7 (SD: 50.1) n=230 | 62.9 (SD: 48.4) n=194 | 70.2 (SD: 45.8) n=245 | 0.007 | 69.0 (SD: 46.4) n=261 | 0.749 |
| Mean reported distance to ORS access point (km) by those with a child who had diarrhoea in the preceding 2 weeks | 8.5 (SD: 11.7) n=112 | 5.5 (SD: 10.5) n=122 | 4.9 (SD: 6.2) n=172 | 0.110 | 5.5 (SD: 4.4) n=180 | 0.479 |

Figures in bold font denote statistically significant values.

*P values are for the unadjusted ORs comparing matched districts and account for within-site correlation of outcomes for proportions; t-tests were used to compare means between matched districts.

ORS, oral rehydration salts.
Given that zinc coverage was <1% at baseline across all districts, evidence of the trial’s success or failure was determined by the difference in ORS and zinc coverage between the matched intervention and comparator districts at endline. The primary endpoint was calculated as the proportion of diarrhoea cases within the previous 2 weeks treated with ORS and zinc among children aged <5 years, expressed as a percentage per district. The effect of the intervention is the ‘delta’ of ORS and zinc treatment between each set of intervention and comparator districts at endline. We used a generalised linear model with Poisson distribution to estimate the relative risk of combined ORS and zinc use. Variance of beta coefficients were adjusted for within-site correlation (table 2).

To assess the impact of the trial on ORS coverage (with or without zinc), a secondary, difference-in-differences (DiD) analysis was performed to compare preintervention and postintervention levels of ORS use (table 3). As zinc use was close to nil at baseline, a DiD analysis to test the change in combination therapy (ORS and zinc) was deemed inappropriate. One of the key advantages of the DiD approach is that baseline characteristics, including levels of the outcome of interest, do not need to be comparable at baseline, as the method compares differences over time in the treatment group to those in the comparator.52

The Wald test for the interaction term from this model shows whether there is a statistically significant difference between odds ratios (ORs) in the intervention versus comparator districts (ie, DiD analysis). In addition, we present the DiD estimator53 for each set of intervention and comparator districts, as well as a pooled analysis, which compares outcomes across both intervention districts combined and both comparator districts combined. Logistic regression with time (preintervention vs postintervention), study arm (intervention vs comparator), and their interactions was used to assess the ORs for ORS use comparing intervention versus comparator districts (table 4). Robust
Processes and systems

Table 4  Impact of emulating private-sector value-chains: difference and change in use of ORS among intervention and comparator site households, rural Zambia, 2012–2013

| Comparison | OR (95% CI) | P value |
|------------|------------|---------|
| Intervention (Kalomo) versus comparator (Monze) at baseline | 0.56 (0.37 to 0.85) | 0.006 |
| Intervention (Kalomo) versus comparator (Monze) at endline | 3.67 (1.77 to 7.61) | 0.000 |
| Intervention (Kalomo) endline versus baseline | 4.71 (2.68 to 8.26) | 0.000 |
| Comparator (Monze) endline versus baseline | 0.72 (0.43 to 1.19) | 0.200 |
| Time by study-arm interaction | 6.55 (2.96 to 14.49) | 0.000 |
| Intervention (Katete) versus comparator (Petauke) at baseline | 1.06 (0.74 to 1.52) | 0.749 |
| Intervention (Katete) versus comparator (Petauke) at endline | 1.57 (0.78 to 3.15) | 0.208 |
| Intervention (Katete) endline versus baseline | 1.07 (0.65 to 1.78) | 0.787 |
| Comparator (Petauke) endline versus baseline | 0.73 (0.46 to 1.15) | 0.173 |
| Time by study-arm interaction | 1.48 (0.69 to 3.17) | 0.317 |

Adjusted for within-site correlation using the robust variance estimate.
Figures in bold font denote statistically significant values.
ORS, oral rehydration salts.

Table 5 Diarrhoea prevalence, ORS and zinc coverage, ORS coverage, and ORS source in the intervention (Kalomo and Katete) versus comparator districts (Monze and Petauke, respectively) at endline, 2013

| Characteristic | Southern province | Eastern province | P value* |
|----------------|------------------|------------------|---------|
| Proportion of households with children aged <5 years who had diarrhoea in the previous 2 weeks (%) | | | 0.967 |
| Kalomo (intervention) n=614 | 28.5 | 31.0 | 0.084 |
| Monze (comparator) n=604 | 28.6 | 25.6 |
| | SD=45.1 | SD=46.2 |
| | n=614 | n=604 |
| ORS with zinc use in children aged <5 years with diarrhoea (%) | | | <0.001 |
| Kalomo (intervention) n=142 | 46.9 | 46.3 | <0.001 |
| | SD=50.0 | SD=49.9 |
| | n=175 | n=194 |
| Monze (comparator) n=138 | 1.7 | 0.6 | 0.224 |
| | SD=13.1 | SD=7.9 |
| | n=173 | n=162 |
| Proportion of children aged <5 years with diarrhoea who used ORS (with or without zinc) (%) | | | <0.001 |
| Kalomo (intervention) n=142 | 81.1 | 71.1 | <0.001 |
| | SD=38.8 | SD=45.2 |
| | n=175 | n=194 |
| Monze (comparator) n=138 | 54.9 | 61.7 | 0.084 |
| | SD=49.9 | SD=48.8 |
| | n=173 | n=162 |
| Caregivers with children aged <5 years who had diarrhoea in the 2 weeks preceding the survey who obtained ORS from the public sector (%) | | | <0.001 |
| Kalomo (intervention) n=142 | 40.1 | 34.1 | <0.001 |
| | SD=49.2 | SD=47.6 |
| | n=142 | n=138 |
| Monze (comparator) n=138 | 96.8 | 99.0 | 0.084 |
| | SD=17.9 | SD=10 |
| | n=95 | n=100 |

Figures in bold font denote statistically significant values.
*P values are for the unadjusted risk ratio comparing matched districts and account for within-site correlation of outcomes for proportions.
ORS, oral rehydration salts.

variance estimation was used to account for within-site correlations of outcomes.54–56 Data on key social and demographic characteristics are also presented to show the comparability of the intervention and comparator districts over time (baseline vs endline) (tables 1 and 5). All analyses were conducted using STATA V.13.

Informed consent was obtained from all respondents prior to survey administration through signature or other marking. In Zambia, the age of consent is 16.57 Assent was obtained for caregivers under the age of 16, with consent provided by their spouse or legal guardian.

RESULTS
The surveys sought comparability between intervention and comparator districts at baseline, across various diarrhoea-related variables (table 1). No significant differences across these variables were noted between intervention and comparator districts, other than baseline coverage of ORS between Kalomo and...
Monze. There was a statistically significant higher level of ORS use (with or without zinc) in Monze (62.9%) compared with Kalomo (48.7%) (p=0.007) prior to the intervention.

The difference between intervention and comparator districts at endline is shown in table 5. Other than the distance to a treatment access point, none of the baseline characteristics presented in table 1, and not reflected in table 5, showed any significant change. At baseline, almost all ORS access was via the public sector in all districts, while the use of zinc with ORS was <1%. Due to the shift in the point of access, from the public to the private sector (as demonstrated by the proportion of caregivers who obtained ORS from the public sector), the mean distance to access ORS decreased for those using the ORSZ co-pack. The reduction found in the intervention districts was assessed by comparing the distance travelled to the nearest health centre within the intervention districts at baseline with the distance travelled to the nearest shop selling the ORSZ co-pack at endline. The average distance travelled decreased from 8.5 to 3.3 km in Kalomo and from 4.9 to 1.8 km in Katete.

Our primary analysis showed that both intervention districts had significant increases in the use of ORS with zinc, to 46.9% and 46.3% in Kalomo and Katete, respectively, while utilisation in the comparator districts remained very low, staying similar to baseline levels (table 5, figure 4), at 1.7% and 0.6% in Monze and Petauke, respectively. The unadjusted risk ratio (RR) for utilisation of ORS with zinc when comparing Kalomo with Monze was 27.0 (95% CI 10.6 to 69.1, p<0.001). The unadjusted RR for utilisation of ORS with zinc when comparing Katete with Petauke was 75.2 (95% CI 10.3 to 547.7, p<0.001) (table 2).

Our secondary analysis used a DiD approach to compare the change in total ORS use (with or without zinc) between baseline and endline, in the intervention versus comparison districts. The DiD analysis is summarised in table 3. It shows the proportion of children aged <5 years who were given ORS in each district at both baseline and endline, the differences between each set of intervention and comparator during the preperiod- and postperiod, and provides the DiD estimator. The application of a DiD estimator permitted isolation of the effect of the overall approach within our quasi-experimental design. The analysis indicated that the intervention was associated with a significant overall increase in the use of ORS in the intervention district of Kalomo compared with its comparator, Monze, with a DiD estimator representing a 40% increase in ORS coverage (p<0.001). The odds of ORS use were 3.67 times higher (95% CI 1.77 to 7.61, p<0.001) in Kalomo than in Monze at endline, whereas they were significantly lower at baseline (OR 0.56, 95% CI 0.37 to 0.85, p=0.006) (table 4). The Wald test for the interaction term (time by study-arm) from this model (table 4) verified the significance of the estimator in table 3 and confirmed the significant difference between ORS in Kalomo vs Monze.

With reference to the second intervention district (Katete) and its comparator (Petauke), the DiD analysis found a non-significant DiD estimator, representing just an 8.2% increase in ORS coverage (p=0.178) (table 3). The odds of ORS use were not significantly different in Katete compared with Petauke at either baseline (OR 1.06; 95% CI 0.74 to 1.52; p=0.749) or endline (OR 1.57; 95% CI 0.78 to 3.15; p=0.208), with the proportion of ORS use staying relatively the same in Katete and decreasing in Petauke, although this
Processes and systems

decrease was not statistically significant. ORS use was already relatively high at baseline in these districts and no major increase in ORS use was observed, although a shift in point of access and towards increased use of the combined ORS and zinc therapy was observed. Within each district, the odds of ORS use comparing baseline with endline were only significantly greater in Kalomo, postintervention (OR 4.71, 95% CI 2.68 to 8.26, p<0.001), while the odds of use remained similar in Katete (OR 1.07, 95% CI: 0.65 to 1.78, p=0.787) and decreased, although not significantly, in both comparators (table 4).

With regard to ORS access, there was a clear shift to the private sector, and specifically to the use of the ORSZ co-pack. The proportion of ORS users who obtained ORS from the public sector decreased from close to 100% (table 1) to 40.1% and 34.1% in Kalomo and Katete, respectively, while ORS continued to be sourced solely from the public sector in both comparator districts (table 5). This represented a significant shift from the public to the private sector in the intervention districts of 60% and 66% in Kalomo and Katete, respectively, which may reduce some of the burden on the public health system. A decrease from baseline was also seen in the household prevalence of diarrhoea across all districts; however, there was no significant difference between the paired intervention and comparator districts.

**DISCUSSION**

The science of applying business principles to global health is evolving. Here, we have provided evidence that by emulating private-sector value-chains of FMCGs and applying the lessons learnt to the introduction of an innovative ORSZ co-pack, a significant increase in coverage of ORS and zinc at the community level can be achieved. The creation of the value-chain for the ORSZ co-pack comprised three core pillars. The first pillar involved the concurrent development of a public health commodity, based on human-centred design,45 with its value-chain (ie, simultaneous consideration of both supply and demand elements of access). The second pillar involved tapping into existing, local networks of private-sector actors, including a local manufacturer, district-level general wholesalers and community-level general retailers, all of whom made a gross margin from selling the product. The third pillar focused on demand-generation activities, including social marketing (radio, posters, community events, plays, testimonials, etc), working with regional health centres and CHWs, training retailers and CHWs, and targeted distribution of vouchers.

These pillars were enabled by drawing on relevant expertise and establishing partnerships across existing organisations and sectors to generate maximum value. In this way, the value-chain concept adopts a systems approach to inherently address the core barriers to reducing childhood deaths from diarrhoea, namely access, production, distribution and promotion.16

Our intervention proved feasible in multiple rural communities in two distinct geographical areas, that is, the southern and eastern provinces of Zambia. Given that 60.5% of the Zambian population lives in rural areas,56 we consider that the gains in ORS and zinc coverage observed in our study likely translated to subnational reductions in childhood morbidity and mortality following the subsequent national scale-up of the model via private and public channels. This trial also informed design modifications to the ORSZ co-pack, which, together with economies of scale, eliminated the need to subsidise the ex-factory price of the product. The experience of this trial led the Ministry of Health in Zambia to add co-packaged ORS and zinc to the national Essential Medicines List. This led to the production of a government-branded version of the co-pack, which is now distributed via health centres. According to the most recent DHS, 2018, 67% of children with diarrhoea received ORS from a sachet, and 34% received a combination of ORS and zinc.59

Integrated community case management (iCCM) is an alternative strategy for delivering ORS and zinc to remote, hard to reach communities; however, we observed little evidence of iCCM, and by 2016, 3 years after the ColaLife trial concluded, just 15% and 5% of iCCM zinc commodities ordered in the intervention and control districts, respectively, had been received.60 No effect of iCCM on the proportion of children appropriately treated for diarrhoea was noted, and thus iCCM is not considered to have been a potential confounder.

It should be noted that the effects on ORS and zinc coverage were mostly driven by an increase in zinc use, completely so in Katete. Zinc was essentially introduced as a new product, whereas ORS may have already been experiencing some ceiling effects, hence little change in Katete between the baseline and endline. New products have different behavioural change implications to those of existing products, and ORS use was already quite high at baseline (eg, 70.2% in Katete).

Previous research has demonstrated that optimal treatment with ORS and zinc, as facilitated here by the innovative design of our ORSZ co-pack and establishment of its value-chain, is associated with reductions in the inappropriate use of antibiotics and intravenous fluids to treat diarrhoea.42 61–64 Estimates suggest that if universal coverage of ORS and zinc combination therapy were achieved, 75% of diarrhoea-related deaths could be averted.16 65 The introduction of co-packaged ORS and zinc has been recommended as a promising strategy for scaling up the use of these interventions.3 15 16 66 Other studies have also demonstrated the advantages of co-packaging ORS and zinc in both public and private settings, including improved marketing and use of the combined therapy, reduced diarrhoea burden, fewer hospitalisations and reduced
antibiotic use. Subsequent to this trial, and based on some of its evidence, WHO amended its model Essential Medicines List in 2019 to specify co-packaged ORS and zinc for the treatment of childhood diarrhoea.

Vouchers kick-started the value-chain by ensuring initial demand from caregivers and helped provide retailers with the confidence to purchase the new kits from wholesalers and bring the kits into their communities. It also allowed caregivers to try a new product without having to pay for it, thus helping to create a sense of value around the product. In addition, the perceived commercial risk associated with entering the market for low-cost public health products can deter potential manufacturers. Vouchers represent an effective means to entice new entrants by building market demand and allowing the product to gain traction; they can achieve this without distorting the value-chain. Rather, they strengthen it, by putting value in the hands of the customer. This has the effect of strengthening existing distribution channels rather than undermining them. Public funds can be impactful in facilitating these types of market-shaping initiatives, as well as the associated research and development that is necessary, prior to transferring full ownership of the value-chain to the private sector for long-term sustainability.

Limitations
Our study had several limitations. While the use of vouchers perhaps makes it more difficult to assess whether a purely private-sector approach was responsible for the increase in coverage (ie, the value-chain approach described minus the vouchers) or whether the increase was driven by a shop-based, voucher-enabled subsidy, what is clear is that emulation of a value-chain approach can move a product from point A to a rural point B. We can also be confident that if, within the context of an established value-chain, governments or donors were to subsidise the ex-factory cost of commercial ORSZ co-packs and make them available through local, rural retailers, coverage of the recommended combination therapy is likely to increase.

The intensity of community engagement differed between the two intervention districts, which may have affected the levels of uptake across the intervention districts. From April to September 2013, there were 1195 promotional events held, 68% and 32% in Kalomo and Katete, respectively. While promotion in Katete was initially stronger, over the longer-term the Kalomo field staff were more effective both in terms of messaging and post-March 2013 sales support, following the cessation of voucher distribution. This may account for some of the variability in effects seen in the two intervention districts, particularly with regard to ORS use with or without zinc, which increased in Kalomo while remaining relatively constant in Katete.

While our study design could not disaggregate which component(s) of the model contributed most to the increased uptake of ORS and zinc and which should be improved or removed, this type of systems package of interventions has a theoretical basis for being stronger than its component parts. Recent research focused on improving access to diarrhoea treatments in Nigeria, for example, also found that shaping the market system for ORS and zinc was effective in equitably improving coverage of the combination therapy. Future research may be conducted to assess the specific contributions of individual components of such an approach. This might include, for example, comparing and contrasting the most cost-effective methods for generating (and sustaining) demand for a newly introduced health commodity in rural markets (eg, vouchers vs other mechanisms). However, lending strength to previous recommendations, it is clear that simultaneous stimulation of supply and demand, with coordinated marketing campaigns and while supporting existing manufacturers and distributors, can indeed help to ensure widespread availability and use. Existing networks of private-sector players (eg, wholesalers, community-level retailers) can be leveraged and trained to provide access to basic health commodities at the community level. These secondary distribution channels, beyond district towns, already exist and can help overcome distribution bottlenecks seen in the public sector. For this trial, we contracted Medical Stores, on commercial terms, to distribute the product to district-level wholesalers; however, this function could be filled by any number of distribution partners. Also, while this study focused on rural sites, similar issues around access to and use of ORS and zinc also occur in urban areas of Zambia.

Introducing complementary points of access to the public sector can serve to improve community case management of diarrhoea at the household level. However, to assess progress/success in the management of diarrhoea, there is a need to go beyond ORS and zinc coverage data. Additional research is needed around the detailed and rational use of ORS and zinc at the household level. This would include various factors, including whether ORS is correctly prepared and used. These aspects will be explored further in a subsequent publication. Other important elements of the model should be evaluated from a process perspective. With obvious implications for feasibility and sustainability, these include the quality of information/services provided by general, commercial retailers; the role of project management to catalyse the value-chain; and consideration of enabling factors, such as support of private-sector initiatives by national authorities and the cooperation and capacity of local private-sector manufacturers (especially if local production is emphasised). Gaining greater insights into the role such factors play in contributing to the overall value of this type of “total-market approach” will be important for
any future adaptations of the model. It would also be helpful to analyse the impact of the ORSZ co-pack on household-level costs and conduct a cost-effectiveness analysis.

In conclusion, limited access to ORS and zinc, the globally recommended treatment for diarrhoea in children aged <5 years, remains a problem in LMICs. This study tested an approach including the creation of a value-chain to introduce a co-pack containing ORS and zinc for diarrhoea treatment in rural Zambia. Each phase of the study is presented in detail, including the full chain of activities relating to the introduction of the ORSZ co-pack. The implementation of this innovative approach improved the coverage of ORS and zinc providing a feasible approach to contribute to the reduction of child deaths from diarrhoea in rural Zambia and communities across the world with similar conditions. By employing techniques used for the development and distribution of FMCGs, primarily appropriate product-design coupled with value-chain creation, the private sector can be engaged to markedly improve ORS and zinc coverage at the community level.

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Acknowledgements We would like to extend our thanks to all participants and partners who contributed to this study. We would also like to acknowledge advisory support provided by William Brieger, Gayane Yenokyan and Beth-Anne Pratt. Editorial support, according to Good Publication Practice guidelines, was provided by Adam Bodley.

Contributors RR, SB and JB conceived and designed the study. SB, JB and RR were responsible for the design, coordination and implementation (in collaboration with partners including the Ministry of Health, Pharmanova, UNICEF, Medical Stores, SAB Miller, PI Global, etc) of technical aspects of the trial, including the ORS and zinc co-pack (Kit Yamoyo). RR and ST were co-PI’s and led the data-collection and fieldwork for the household surveys. RR performed the analyses and wrote the first draft of the manuscript. REB reviewed the manuscript and served as an ongoing advisor to RR. All authors contributed to the revision of the manuscript and have approved the final version to be published.

Funding Funding for this work was provided by the UK’s Foreign, Commonwealth & Development Office (FCDO; UK Aid; formerly DFID), Johnson and Johnson Corporate Citizenship Trust, and Grand Challenges Canada.

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Competing interests SB and JB are co-Founders of ColaLife, a not-for-profit UK charity set-up solely for the purpose of conducting this global health innovation work. RR served as Public Health Advisor and Principal Investigator for ColaLife.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Implementation of the project was authorised by national and district government health administrations and through local chiefs. Ethics approval was obtained from ERES Converge in Zambia (IRB No. 00005948; Ref. No. 2012-Jun-002), with approval for secondary analysis from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified household survey data from the ColaLife Operational Trial Zambia (COTZ) are available upon request from ColaLife, UK charity number 1142516.

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