Antibiotic stewardship using ePOCT+, a digital health clinical decision support algorithm for paediatric outpatient care: results from the DYNAMIC Tanzania cluster randomized controlled trial

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Abstract

Excessive antibiotic use and antimicrobial resistance are major global public health threats. We developed ePOCT+, a digital Clinical Decision Support Algorithm in combination with C-reactive protein test, haemoglobin test, pulse oximeter and mentorship, to guide healthcare providers in managing acutely sick children under 15 years old. To evaluate the impact of ePOCT + compared to usual care, we conducted a cluster-randomized controlled trial in Tanzanian primary care facilities (NCT05144763). Over 11 months, 23 593 consultations were included in 20 ePOCT + health facilities, and 20 713 in 20 usual care facilities. Antibiotics were prescribed in 23.2% of consultations in ePOCT + facilities, and 70.1% in usual care facilities (adjusted difference, -46.4%, 95% confidence interval (CI) -57.6 to -35.2). Day 7 clinical failure in ePOCT + facilities was non-inferior to usual care facilities (adjusted relative risk 0.97, 95% CI 0.85 to 1.10). Using ePOCT + could help address the urgent problem of antimicrobial resistance by safely reducing antibiotic prescribing.

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Introduction

Bacterial antimicrobial resistance (AMR) was responsible for 1.27 million deaths in 2019, with the highest burden in Sub-Saharan Africa.[1] This is as many deaths as malaria and HIV combined. Inappropriate and excessive prescription of antibiotics represents one of the primary contributors of AMR.[2–4] In Tanzania and many resource constrained countries, more than 50% of sick children receive antibiotics when visiting a health facility,[5–8] with 80–90% of such antibiotics prescribed at the outpatient level[6,9,10] and most deemed innapropriate.[5,9–11] Antibiotic use and AMR are projected to increase over the next years, indicating the urgency to take action.[12–14] Accordingly, the World Health Organization (WHO) has declared AMR as 'one of the biggest threats to global health, food security and development today'.[15]

Electronic Clinical Decision Support Algorithms (CDSAs) are digital health or mobile health (mHealth) tools that guide healthcare providers on what symptoms and signs to assess, advise on what tests to perform, and finally propose the appropriate diagnoses, treatments and managements.[16,17] Previous efficacy studies under controlled research conditions have shown the potential for digital CDSAs to significantly reduce antibiotic prescription in children 2 to 59 months old.[18,19] However, many close to real-world studies have shown little to no reduction in antibiotic prescription.[20–22] In addition, many of the close to real-world studies have a number of methodological limitations as health facilities were not randomized, and/or safety was not evaluated,[16,22,23] emphasizing the need for more evidence on the impact of CDSAs on antibiotic prescription. Finally, poor uptake remains a challenge with previous and existing CDSAs.[24,25]

We developed ePOCT+, a novel CDSA with point-of-care tests, to address these challenges.[26] The scope of ePOCT + was expanded from previous versions of the CDSA to include infants under 2 months and children up to age 14 years old, and to address syndromes and diagnoses not considered by other CDSAs.[18,27] The aim of this study was to evaluate the impact of ePOCT + compared to usual care on antibiotic prescription and day 7 clinical outcome, in a pragmatic, cluster randomized controlled trial in acutely sick children under 15 years of age presenting to Tanzanian primary care facilities.

Results

Baseline characteristics of health facilities and patients

A total of 68 out of 259 health facilities from the participating councils met eligibility criteria (Fig. 2). A stratified random sampling process identified 40 health facilities for inclusion in the study (24 in Morogoro region, and 16 in Mbeya region), which were randomized 1:1 to ePOCT+ (intervention) or usual care (control). Between 1 December 2021, and 31 October 2022, 59 875 children were screened for inclusion, and 44 306 (74%) consultations were enrolled (23 593 in ePOCT + health facilities, and 20 713 consultations in usual care health facilities). The first health facilities started enrolling patients on 1 December 2021, and the last health facilities started enrolling patients on 13 April 2022. A total of 28 243 unique patients were enrolled with an average of 1.6 consultations per patient over the duration of the study. Among those enrolled in the intervention health facilities, 17 985 (76.2%) consultations were managed using ePOCT+, and day 7 outcome was ascertained in 20 355 consultations (86.3%). In usual care health facilities, 18 937 (91.4%) consultations had final treatment documented in the eCRF and 17 292 consultations (83.5%) had day 7 outcome ascertained. IT problems and power outages were reported by research assistants in respectively 293 (7.3%) and 245 (6.1%) health facility-days in ePOCT + facilities, and 160 (4.1%) and 245 (6.1%) health facility days in usual care facilities. Both issues contributed to children not being able to be enrolled in the study.

Intervention health facilities saw similar numbers of consultations, but had a slightly lower Service Availability and Readiness Assessment Pediatric score (Table 1).[28] Patients in both study arms were similar in age, sex, type of consultation and previous hospitalization (Table 1). Young infants less than 2 months of age in the intervention health facilities presented more frequently for fever, convulsions or lethargy, and slightly less for respiratory conditions, while patients 2 months and above had a similar distribution in presenting complaints (Table 2). Age, phone availability, and level of health facility differed between patients with and without day 7 outcome ascertained (Supplementary material table S1and S2). Patients managed and not managed per-protocol were similar, except for the level of health facility (Supplementary material table S3).

Table 1
Baseline characteristics of enrolled participants and health facilities

Health facilities	ePOCT+ (*n* = 20)	Usual Care (*n* = 20)
Level of health facilit, *n* Dispensaries	16	16
Health centres	4	4
Region, *n* Morogoro	12	12
Mbeya	8	8
Average number of enrolled patients per health facility per month, median (IQR)	127 (IQR 101; 199)	136 (IQR 73; 163)
Service Availability and Readiness Assessment[a]: General Service Readiness Score, mean (SD)	60.3% +/-10.8	63.7% +/-9.4
Pediatric Score, mean (SD)	55.9% +/-10.8	64.9% +/-10.6
Participants	**ePOCT+ (n = 23,593)**	**Usual Care (n = 20,713)**
Sex: Female, % *(n)*	51.2% (12,085)	51.3% (10,075)
Age in days, median (IQR)	583 (IQR 263; 1,202)	555 (IQR 246; 1,189)
Age group, % *(n)* 0 to < 2 months	4.0% (954)	5.0% (1,038)
2 to < 60 months	84.1% (19,845)	82.0% (16,984)
5 to < 15 years	11.8% (2,794)	13.0% (2,691)
Type of consultation, % *(n)* New consultation	91.9% (21,680)	90.7% (18,789)
Re-attendance	7.8% (1,841)	9.2% (1,899)
Referral from another health facility	0.3% (72)	0.1% (25)
Hospitalized in the last 14 days, % *(n)*	0.3% (65)	0.4% (73)
Phone number available, % *(n)*	84.0% (19,808)	83.0% (17,186)

Table legend: Participant data from all enrolled patients. Values of standard deviations (SD, after mean values) are preceded by the +/- sign. IQR: Interquartile ranges (after median values).

[a]Scores were calculated based on the proportion of prespecified indicators that were present in each health facility during the assessment of health facilities before the start of the study.[28]

Presenting complaints in < 2 months	ePOCT+ (n = 717)	Usual Care (n = 929)
Fever, convulsions, lethargy	25.7%	13.1%
Respiratory	43.7%	46.8%
Gastrointestinal	22.2%	19.7%
Skin	14.0%	14.5%
Ear/mouth	2.5%	0.9%
Eye	7.0%	5.4%
Feeding / weight	0.3%	1%
Malformation	0.4%	0.4%
Injuries	0.4%	0.1%
Other	6.4%	7.8%
Presenting complaints in > = 2 months to < 15 years	ePOCT+ (n = 17 268)	Usual Care (n = 17 089)
Fever	61.6%	56.9%
Respiratory (cough / difficulty breathing	47.8%	49.4%
Gastrointestinal (diarrhea/vomiting)	23.4%	22.3%
Skin	12.5%	11.9%
Ear/throat/mouth	2.6%	2.3%
Eye	2.1%	2.1%
Genitourinary	1.4%	3.1%
Neurological (Headache, stiff neck)	3%	1.2%
Accident / musculoskeletal (incl. burns, wounds, poison)	1.5%	2.0%
Other	2.1%	4.2%

Table legend: Data from patients for which clinical information was entered into ePOCT + in the intervention arm, and in the eCRF in control health facilities (per-protocol population). Patients may have multiple complaints

Primary outcomes: Antibiotic prescription and clinical failure

Overall antibiotic prescription at initial consultations for the per-protocol analysis was 23.2% (3,806/16,381) in ePOCT + health facilities, and 70.1% (12,058/17,205) in routine care health facilities, which corresponds to an adjusted absolute difference of -46.4% (95% CI -57.6; -35.2) (Table 3, Fig. 3). The adjusted analysis found a 65% reduction in the risk of prescribing an antibiotic at day 0 (aRR 0.35, 95% CI 0.29 to 0.43, p-value < 0.001). Taking a conservative approach by considering that all patients that were not managed per protocol were prescribed an antibiotic (intention-to-treat analysis), antibiotic prescription remained lower in ePOCT + health facilities than in usual care, with an adjusted absolute difference of -34.2%, 95% CI -42.1%, -26.4% (Table S4). When including re-attendance cases, antibiotic prescription reduction was similar, with an adjusted absolute difference of -45.0%, 95% CI -56.3% to -33.6% (Table S5).

The proportion of patients with clinical failure by day 7 was non-inferior in ePOCT + health facilities (3.7% (532/14,396) compared to usual care health facilities (3.8% (543/14,363), with an adjusted relative risk of 0.97 (95% CI 0.85 to 1.10) in the per-protocol complete case population (Table 3, Fig. 3). Clinical failure by day 7 was also non-inferior in the intention-to-treat complete case population (Table S4), when including re-attendance cases (Table S5) and using unadjusted analyses (Table 3, Fig. 3).

Table 3
Antibiotic prescription and clinical outcomes among sick children in the DYNAMIC trial

	ePOCT+, % (n/N)	Usual care, % (n/N)	Intracluster Correlation Coefficient (95% CI)	Crude Difference (95% CI)	Adjusted difference (95% CI)	Crude Relative Risk (95% CI)	p-value	Adjusted Relative Risk (95% CI)	p-value
Primary outcome									
Antibiotic prescription at day 0	23.2% (3,806/16,381)	70.1% (12,058/17,205)	0.3 (0.2; 0.4)	-46.9% (-47.8%; -45.9%)	-46.4% (-57.6%; -35.2%)	0.33 (0.32; 0.34)	< 0.001	0.35 (0.29; 0.43)	< 0.001
Clinical failure by day 7	3.7% (532/14,396)	3.8% (543/14,363)	0.004 (0.001; 0.006)	-0.1% (-0.5% ; 0.4%)	-0.1% (-0.6%; 0.3%)	0.98 (0.87; 1.10)	0.70	0.97 (0.85; 1.10)	0.59
Secondary and exploratory outcomes									
Death by day 7	0.1% (9/14,396)	0.1% (11/14,363)	< 0.001	0.0% (-0.1%; 0.0%)	0.0% (-0.1%; 0.0%)	0.82 (0.34; 1.97)	0.65	0.66 (0.24, 1.84)	0.43
Subjectively worse at day 7[a]	0.3% (41/14,396)	0.3% (40/14,363)	0.002 (0.000; 0.004)	0.0% (-0.1%; 0.1%)	0.0% (-0.1%; 0.2%)	1.02 (0.66; 1.58)	0.92	1.11 (0.71; 1.73)	0.65
Non-referred secondary hospitalizations by day 7	0.4% (57/14,396)	0.4% (50/14,363)	0.001 (0.000; 0.002	0.0% (-0.1%; 0.2%)	0.0% (-0.0%; 0.2%)	1.14 (0.78; 1.66)	0.51	1.14 (0.77; 1.69)	0.52
Hospitalizations by day 7[a]	1.0% (145/14,396)	0.9% (130/14,363)	0.01 (0.01; 0.02)	0.1% (-0.1%; 0.3%)	0.3% (-0.0%; 0.7%)	1.11 (0.88; 1.41)	0.38	1.43 (1.00; 2.05)	0.05
Primary referrals at day 0	1.2% (194/16,381)	1.0% (170/17,205)	0.03 (0.01; 0.04)	0.1% (-0.2%; 0.3%)	0.8% (0.1%; 1.5%)	1.2 (0.98; 1.47)	0.08	2.08 (1.15; 3.74)	0.02
Referral resulting in hospitalization by day 7[b]	16.8% (25/149)	20.3% (29/143)	0.05 (0.00; 0.14)	-3.5% (-5.4%; 12.4%)	-2.8% (-11.8%; 6.2%)	0.83 (0.51; 1.34)	0.44	0.86 (0.53; 1.40)	0.55
Uplanned re-attendance visits by day 7[c]	1.8% (256/14,603)	2.9% (425/14,723)	0.03 (0.01; 0.04)	-1.1% (-1.5%; -0.8%)	-1.0% (-2.8%; 0.9%)	0.61 (0.52; 0.71)	< 0.001	0.67 (0.32; 1.44)	0.31
Additional medication taken after initial consultation up to day 7	7.1% (1,006/14,244)	7.2% (1,017/14,229)	0.006	-0.1% (-0.7%; 0.5%)	-0.9% (-2.1%; 0.4%)	0.99 (0.91; 1.07)	0.78	0.88 (0.74; 1.05)	0.17

Table legend: All data shown for day 0 outcomes are per-protocol, and all data for day 7 outcomes are per-protocol and complete case (day 7 outcomes assessed). Clinical failure by day 7 defined as "not cured" and "not improved", or unscheduled hospitalization as reported by caregivers. Non-referred secondary hospitalizations by day 7 are hospitalizations at least a day after the initial consultation that was not referred by a healthcare provider. Unplanned re-attendance visits by day 7 are return visits between day 1 to 7 that were not proposed by the initial healthcare provider. Adjusted relative risks and differences were estimated using a random-effects logistic regression model adjusting for clustering (health facility and patient), as well as individual (age, sex, complaints, availability of phone) and health facility (council of health facility, level of health facility, average number of patients seen per month at the health facility) baseline characteristics.

[a] Post-hoc exploratory outcome not pre-specified.

[b] Denominator is based on consultations for which a primary referral was proposed and day 7 hospitalization data was ascertained, as such may be less than the total number of primary referrals at day 0.

[c] Including unplanned outpatient and hospitalized re-attendance visits

Secondary and exploratory clinical safety outcomes

There were no significant differences in the proportion of patients who died, were subjectively worse, were hospitalized after the day of the initial consultation without a referral (non-referred secondary hospitalization), all hospitalizations by day 7, or unplanned re-attendance visits (Table 3). There was however a significant reduction in unplanned re-attendance visits by day 7 in unadjusted analyses. The proportion of patients who died (0.1%) or were hospitalized (1.0%) were low in both arms. Results in the intention-to-treat population, and when including re-attendance visits were similar (Table S4 and S5).

Additional medications by day 7 and antibiotic prescription over time

At day 7 (range 6–14), additional medicines were taken after the initial consultation in a similar proportion of patients between study arms (7.1% vs 7.2% in intervention vs control health facilities, Table 3). When evaluating evolution of mean antibiotic prescription rates over time, it appears to decrease over time in ePOCT + health facilities, while no change was found in usual care facilities (Figure S1).

Referral and hospitalizations

Healthcare providers identified 3.6% (582/15,799) of cases as having a severe diagnosis in ePOCT + facilities compared to 2.6% (453/17,205) in usual care facilities (per-protocol in initial cases). The proportion of cases referred for hospitalization was higher in ePOCT + facilities (1.2%) than in usual care facilities (1.0%) (aRR 2.08 (95% CI, 1.15 to 3.74), Table 3). The proportion of children referred that resulted in hospitalization was low and similar in both study arms (Table 3). The proportion of cases referred to specialized outpatient clinics (malnutrition clinic, tuberculosis investigation, HIV clinic) was low and similar between ePOCT + and usual care health facilities (Table S6).

Subgroup analyses (sex, age, complaints)

The effect of the intervention on antibiotic prescription at day 0 was more pronounced in children presenting with respiratory complaints (absolute difference – 62.1%; 95% CI -63.3%, -60.9%) and the 2–59 month age group (absolute difference – 48.9%; 95% CI -49.9%, -47.9%) (Fig. 4 and Table S7). Antibiotic prescription was reduced by at least 25 percentage points in all subgroups, with the smallest reduction found in infants under 2 months old (absolute difference – 25.5%; 95% CI -30.3%, -20.6%). Young infants less than 2 months old had the largest reduction in day 7 clinical failure (aRR 0.61; 95% CI 0.37, 1.00; p-value 0.05) (Fig. 5 and Table S8).

Discussion

In this cluster randomized controlled trial involving 44 306 sick children under 15 years of age in Tanzania, the use of the ePOCT + digital clinical decision support algorithm (CDSA) package resulted in a 3-fold reduction in the likelihood of a sick child receiving an antibiotic prescription compared to children in usual care facilities. Despite substantially fewer antibiotic prescriptions, clinical failure did not increase in intervention facilities.

The reduction of antibiotic prescription associated with the ePOCT + intervention in our study is consistent with our previous research with CDSAs in Tanzania in more controlled research settings.[18,19,29] However, the results differ from other studies evaluating CDSAs implemented in routine health programs in Nigeria, Afghanistan, and Burkina Faso, which found little to no reduction in antibiotic prescription.[20–22, 30] There are a number of differences that may explain the divergent results. First and foremost, the clinical algorithm of ePOCT + differs from other CDSAs. It notably has a wider scope including additional conditions and point-of-care tests such as CRP, not included in IMCI.[26] A randomized controlled trial comparing two different CDSAs found differences in the impact of antibiotic stewardship due to the addition of CRP and other algorithm modifications, demonstrating that not all CDSAs are equal.[18] Other differences that may explain the divergent results include 1) differences in the supportive training and mentorship provided, 2) disease epidemiology, and 3) healthcare provider skills and adherence. The extent of the impact on antibiotic stewardship in our study is also greater than those observed in other antibiotic stewardship studies that included one single intervention rather than an intervention package.[31,32] ePOCT + integrates multiple proven antibiotic stewardship interventions together, including clinical decision support,[18,19,29] the use of point-of-care CRP tests,[33] pulse oximeter,[34] and continuous quality improvement mentorship support with data feedback to healthcare providers utilizing benchmarking of health facilities.[35,36]

Clinical failure was not higher in patients managed in ePOCT + health facilities, despite a significant reduction in antibiotic prescription in line with other antibiotic stewardship studies.[33] Similarly the proportion of children who died, were hospitalized without referral, or had unplanned re-attendance visits were not higher. While previous CDSA studies were able to demonstrate significant reductions in clinical failure, the current trial was not powered to do so.[18,19,21] Nonetheless, the greatest benefit on clinical cure compared to usual care was observed in the subgroup of under 2 month olds, important results given that this population represents more than 50% of mortality in under 5 year olds.[37]

Our study possesses several strengths that contribute to its robustness. Firstly, we employed a cluster randomized controlled study design, which was adequately powered to assess non-inferiority of clinical failure. Secondly, the implementation of our intervention encompassed a wide range of epidemiological settings, including both rural and urban areas, with varying levels of malaria transmission and facilities such as dispensaries and health centres. Moreover, our study employed comprehensive patient inclusion criteria that were designed to be inclusive. By incorporating theses inclusive criteria, randomly sampling health facilities for inclusion, and observing consistent effects across subgroups at both the health facility and individual levels, our findings can be generalized to a broader population.

There are several limitations to our study. First, antibiotic prescription data relied on documentation by the healthcare provider, an approach often used in pragmatic trials.[38,39] When using a conservative ITT approach considering that all patients for which treatment was not documented were considered to have been prescribed an antibiotic, ePOCT + still reduced antibiotic prescription considerably (table S4). Second, despite multiple phone calls and home visits, 15% of cases were lost to follow up, consistent with that found in similar studies (13–25%).[40–42] To account for potential biases in loss to follow-up, we adjusted the final model for baseline variables associated with missing outcome data, analogous to performing multiple imputation in the case of a single endpoint. Third, the fact that a child has not improved after day 7 sometimes reflects the natural course of the disease, rather than the poor quality of care at the initial consultation, and may not therefore be expected to be influenced by the intervention for all clinical syndromes. To show an effect on more severe outcomes such as secondary hospitalization or death would require a very large sample size due to the rarity of the event at the primary care level. Further complicating assessment of these severe outcomes are challenges linked to referral, and quality of care at admitting hospitals.

In conclusion, the ePOCT + electronic clinical decision support algorithm (CDSA) in association with point-of-care tests (CRP, haemoglobin, pulse oximeter) and mentorship support informed by clinical-practice data, safely and substantially reduced antibiotic prescribtion in sick children less than 15 years presenting to primary care facilities in Tanzania. Widespread implementation of ePOCT + could help address the urgent problem of antimicrobial resistance by reducing excessive antibiotic prescription in sick children while maintaining clinical safety.

Online Methods

Study design and setting

The DYNAMIC Tanzania study was a pragmatic, open-label, parallel-group, cluster randomized trial conducted in 40 primary health facilities in Tanzania. The health facility was the unit of randomization, since the intervention was targeted at the health facility level.

Study sites were purposefully chosen to represent a variety of health care and epidemiological settings within 5 councils in the Mbeya and Morogoro region, with a total population in those councils of 1,701,717.[43] Two councils were semi-urban (Mbeya city and Ifakara Town councils), while the three otherswere rural (Mbeya, Ulanga and Mlimba district councils). 42.8% of the Tanzanian population is less than 15 years old.[44] The malaria prevalence in febrile children age 6–59 months is 5.8% in the Morogoro region, and 3.4% in the Mbeya region.[45] HIV prevalence among children less than 15 years old is 0.5% in both regions.[46] Health care for acute illnesses at government or government designated primary health facilities are free of charge for children under 5 years, including the cost of medications such as antibiotics. For patients above 5 years, health care expenses are at the charge of the patient, unless they have a health insurance plan (around 10% of Tanzanians).[47]

Inclusion & Ethics

Ethical approval

was obtained in Tanzania from the Ifakara Health Institute (IHI/IRB/No: 11-2020), the Mbeya Medical Research Ethics Committee (SZEC-2439/R.A/V.1/65), the National Institute for Medical Research Ethics Committee (NIMR/HQ/R.8a/Vol. IX/3486 and NIMR/HQ/R.8a/Vol. IX/3583), and in Switzerland from the cantonal ethics review board of Vaud (CER-VD 2020–02800). The study was registered on ClinicalTrials.gov number NCT05144763, where the trial protocol and statistical analysis plan can be found.

The study design and implementation was developed collaboratively between the Ifakara Health Institute, Mbeya Medical Research Centre, Swiss Tropical and Public Health Institute and the Centre for Primary Care and Public Health, University of Lausanne, based on feedback from stakeholders, patients and healthcare providers involved in our similar trials in Tanzania.[18,19,29] Over 100 community engagement meetings with over 7 000 participants were conducted before and during the study.

Participants

Primary care health facilities (dispensaries or health centres) were eligible for inclusion if they performed on average 20 or more consultations with children 2 months to 5 years per week, were government or government-designated health facilities, and were located less than 150 km

from the research institutions. Acute outpatient care is routinely provided by nurses and clinical officers in primary health facilities, while medical doctors provide care on certain occasions at health centres. Clinical officers, the principal health providers at primary health facilities, are non-physician health professionals with 2–3 years of clinical training following secondary school.[48]

Infants and children aged between 1 day old and under 15 years of age seeking care for an acute medical or surgical condition at participating health facilities were eligible. Children presenting solely for scheduled consultations for a chronic disease (e.g. HIV, tuberculosis, malnutrition), or for routine preventive care (e.g. growth monitoring, vaccination) were not eligible. Written informed consent was obtained from all parents or guardians of participants when attending the participating health facility during the enrollment period.

Sampling, randomization and masking

The 40 health facilities were randomly selected from all eligible health facilities in the participating councils following a 3:2 ratio between health facilities from the Morogoro and Mbeya region (in order to include more health facilities in the higher malaria transmission area). In addition, to include a representative sample of health centres compared to dispensaries, 4 health centres per region were included.

The sampled health facilities were then randomized (1:1), to ePOCT+ (intervention) or usual care (control). Randomization was stratified by region, council, level of health facility (health center versus dispensary), and attendance rate. An independent statistician in Switzerland was provided the list of all eligible health facilities, and performed the computer-generated sampling and randomization. Intervention allocation by the study team was only shared to study investigators in Tanzania once all council leaders confirmed the participation of their selected health facilities. The nature of the intervention did not allow for masking of the intervention to healthcare providers, patients, or study implementers.

Intervention

The intervention consisted of providing ePOCT + with the supporting IT infrastructure, C-reactive protein (CRP) semi quantitative lateral flow test, hemoglobin point-of-care tests (and hemoglobinometer if not already available), pulse oximeter, training and supportive mentorship (Fig. 4). The development process and details of the ePOCT + CDSA, and the novel medAL-reader Android-based application used to deploy ePOCT + were described in detail previously.[26] In summary the clinical algorithm of ePOCT + is based on previous generation CDSAs (ALMANACH and ePOCT),[18,27] international and national clinical guidelines, input from national and international expert panels, and was adapted based on piloting and healthcare provider feedback.[26] Mentorship by the implementation team included visits to health facilities every 2–3 months and communication by phone call or group messages 3–4 times per month, to resolve issues and provide guidance and feedback on the use of the new tools. Results from quality of care dashboards were shared through group messages to give feedback on the use of ePOCT+, a strategy often described as 'benchmarking', allowing healthcare providers to compare their antibiotic prescription, uptake, and other quality of care indicators with other health facilities.[49] Control health facilities provided care as usual, with no access to clinical data dashboards.

All participating health facilities were provided with IT infrastructure to support the tablet based ePOCT + CDSA or in the case of control health facilities, to support the use of tablet based electronic case report forms (eCRF). The IT infrastructure included a tablet for each outpatient consultation room, router, local server (Rasberry Pi), internet, and if needed back up power (battery), or solar system. In addition, weighing scales, mid-upper arm circumference (MUAC) bands, and thermometers were provided to health facilities in both arms if not already available. Healthcare providers from both intervention and control health facilities received equivalent clinical refresher training based on the Integrated Management of Childhood Ilness (IMCI) chartbook. In addition specific training was provided on the use of the ePOCT + CDSA in intervention facilities, and the use of the eCRF in control facilities.

Study procedures

Children seeking care at included health facilities were screened for eligibility by a research assistant between 8:00 to 16:00 on weekdays. If eligible, demographic information was collected and entered in the eCRF (ePOCT + for intervention health facilities, and eCRF for usual care facilities within the data collection system medAL-*reader*). Healthcare providers in the control health facilities managed the patients as usual, but documented the main complaints, anthropometrics and test results (if performed), diagnoses, treatments and referral decision in the eCRF. To harmonize data collection across the intervention and control facilities, the eCRF for the control facilities was also programmed into the medAL-reader platform, but no decision support was provided. Research questions were included in the eCRF to capture if an oral or systemic antibiotic was prescribed, and if the patient was referred for inpatient hospitalization or other outpatient investigations. In intervention health facilities, in addition to the same information collected in the eCRF, symptoms and signs of the patients were recorded in the ePOCT + CDSA during the consultation with the patient. The symptoms and signs entered are used by the ePOCT + CDSA to guide the clinical consultation. Healthcare providers who documented the final treatment for a consultation in ePOCT + or the eCRF were categorized as having been managed per-protocol, as recording of the final treatment is required to complete the ePOCT + CDSA.

All patients were called or visited at their home by research assistants to assess clinical outcomes and their care and treatment seeking behaviour at day 7 (range 6–14 days). Research assistants performing the phone calls were blinded to the intervention status, and were not part of the team enrolling patients at health facilities. Home visits rather than phone calls were conducted if the caregiver of patients did not have a phone number or did not know somebody with a phone near their home, or if research assistants were not able to reach the provided phone number after 5 attempts. The home visits were performed by the research assistants enrolling patients from the same health facility, as such they were not blinded to intervention allocation. Patients who were still sick at follow-up were encouraged to return to a health facility for follow-up care. Day 7 data was recorded using RED Cap web for phone calls, and RED Cap mobile application for home visits.

Outcomes

The co-primary outcomes measured at the individual patient level included: 1) antibiotic prescription at the time of the initial consultation as documented by the healthcare provider (superiority analysis); and 2) clinical failure at day 7 defined as "not cured" and "not improved", or unscheduled hospitalization as reported by caregivers (non-inferiority analysis). Secondary outcomes include unscheduled re-attedance visits at any health facility by day 7, non-referred secondary hospitalization by day 7, death by day 7, and referral for inpatient hospitalization at initial consultation. The intervention was deemed a success if ePOCT + was non-inferior in terms of clinical failure and reduced antibiotic prescription by at least 25%. Pre-specified additional outcomes are outlined in the statistical analysis plan.

Sample size

The sample size was calculated for testing non-inferiority of the clinical failure outcome given that it would require a higher sample size than for the antibiotic prescription co-primary outcome. We assumed a cluster size of 900 patients (average of 150 patients per month x 6 months) based on routine data within the natinoal health management information system, an intraclass correlation coefficient of 0.002, and a clinical failure rate of 3%. To have 80% power to detect an acceptable non-inferiority margin of a relative risk of 1.3, corresponding to 3.9%, we required 19 clusters and 17,100 patients per arm (total patients n = 37,620 assuming 10% loss to follow-up). Given the uncertainty of some of the assumptions, the total number of health facilities was rounded up to 20 clusters per arm.

No interim analysis was planned, however due to lower enrollment than expected, after 8 months of recruitment, we planned an ad-hoc sample size recalculation by an independent statistician to calculate the expected power of the study based on updated parameters. The study team pre-specificied the specifications and approach, documented in an update to the statistical analysis plan.

Statistical analysis

All outcomes were evaluated using random effects logistic regression models using the cluster (health facility) and patient as random effects, with further adjustment using fixed effect terms for randomization stratification factors,[50] and baseline characteristics hypothecized to be associated with the outcome, imbalances between arms, and imbalances between characteristics among patients for whom day 7 data was available and not available (lost to follow-up). These included the patient characteristics of age, sex, presenting complaints (fever, respiratory, gastrointestinal, skin) and phone availability, and the health facility characteristics of care provision level (dispensary versus health center), attendance rate per month and council. A partitioning method was used to separate within- and beween- cluster effects to account for confounding by cluster.[51,52] In the case of too few events, and small variance among health facilities which did not allow the model to converge, the health facility was incorporated in the model as a fixed effect. Adjusted relative risk (aRR) and absolute differences was estimated based on the computed marginal probabilities of the conditional probabilities.[53,54] Formal adjustments were not performed for multiple testing, as adjustments would likely be overly conservative given that the outcomes are not all independent,[55] and variable selection was not based on statistical tests of significance.[56]

Non-inferiority was determined if the upper-limit of the 95% confidence interval (CI) of the adjusted relative risk (aRR) was below 1.3. All analyses based on outcomes from day 0 were performed in the per-protocol population, and outcomes determined at day 7 were performed in the per-protocol and complete case population (only in those for which day 7 outcomes were ascertained) and displayed accordingly unless stated otherwise. The primary analyses were performed on the first visit for an illness, with re-attendance visits (a second visit to a health facility for the same illness) included in exploratory analyses. Prespecified analyses to assess the effect of the intervention in different population groups were performed by sex, age group, and consultation complaint categories (respiratory symptoms, fever, gastrointestinal, skin problem, ear, nose and throat problem). All analyses were performed using Stata v16 and v17.[57]

Declarations

Data availability

De-identified data can be found on https://doi.org/10.5281/zenodo.8043523

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Figures

259 Health facilities assessed for eligibility in eligible councils

191 ineligible
122 wrong type of health facility
69 did not see enough patients per week

68 Eligible health facilities

40 Health facilities randomised

20 clusters in the intervention arm (ePOCT+)

20 clusters in the control arm (routine care)

Child-level information

32 965 children screened

26 910 children screened

9 372 Excluded:
Wrong age (n=673)
Not an acute illness (n=719)
Declined or unable to consent (n=4532)
Child not registered or data issue (n=3448)

6 197 Excluded:
Wrong age (n=461)
Not an acute illness (n=165)
Declined or unable to consent (n=3932)
Child not registered or data issue (n=1639)

23 593 consultations included

20 713 consultations included

5 608 consultations without documented treatment in ePOCT+

1 776 consultations without documented treatment in eCRF

17 985 consultations managed using ePOCT+

18 937 consultations documented in eCRF

1 604 re-attendance consultations

1 732 re-attendance consultations

16 381 initial consulttions managed using ePOCT+ (Per-protocol for day 0 outcomes)

17 205 initial consultations documented in eCRF (Per-protocol for day 0 outcomes)

3 238 lost to follow-up

3 421 lost to follow-up

20 355 consultations with day 7 data (intention to treat for day 7 outcomes)

17 292 consultations with day 7 data (intention to treat for day 7 outcome)

4 523 not using ePOCT+
1 685 re-attendance consultations

1 456 eCRF not filled
1 631 re-attendance consultations

14 396 initial consultations in the day 7 outcome per-protocol and complete case population

14 363 initial consultations in the day 7 outcome per-protocol and complete case population

Figure 1

Health facility and patient flow diagram

Legend: Boxes highlighted in grey correspond to the co-primary outcome populations

A) Antibiotic prescription at day 0

70.1% Usual Care
23.2% ePOCT+
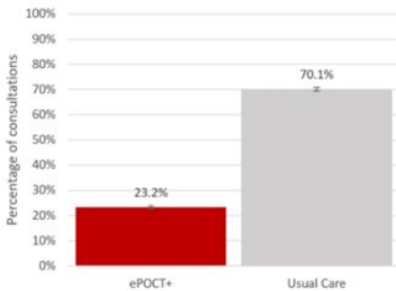
Adjusted Difference, -46.4% (95% CI, -57.6% to -35.2%)

Adjusted relative risk, 0.35 (95% CI 0.29 to 0.43)

B) Non-inferiority plot for clinical failure at day 7

	aRR (95% CI)
ITT (unadjusted)	.99 (0.89, 1.10)
ITT (adjusted)	0.97 (0.86, 1.09)
PP (unadjusted)	0.98 (0.86, 1.10)
PP (adjusted)	0.97 (0.85, 1.10)

1   1.3
Non-inferior   Not non-inferior

Figure 2

Co-primary outcomes

Legend: A) Proportion of antibiotic prescription in ePOCT+ and usual care health facilities; B) Relative risk of day 7 clinical failure between ePOCT+ and usual care health facilities; with non-inferiority pre-specified as an adjusted relative risk of <1.3. ITT: Intention-to-treat; PP: Per-protocol; RR: Adjusted relative risk

A) Antibiotic prescription

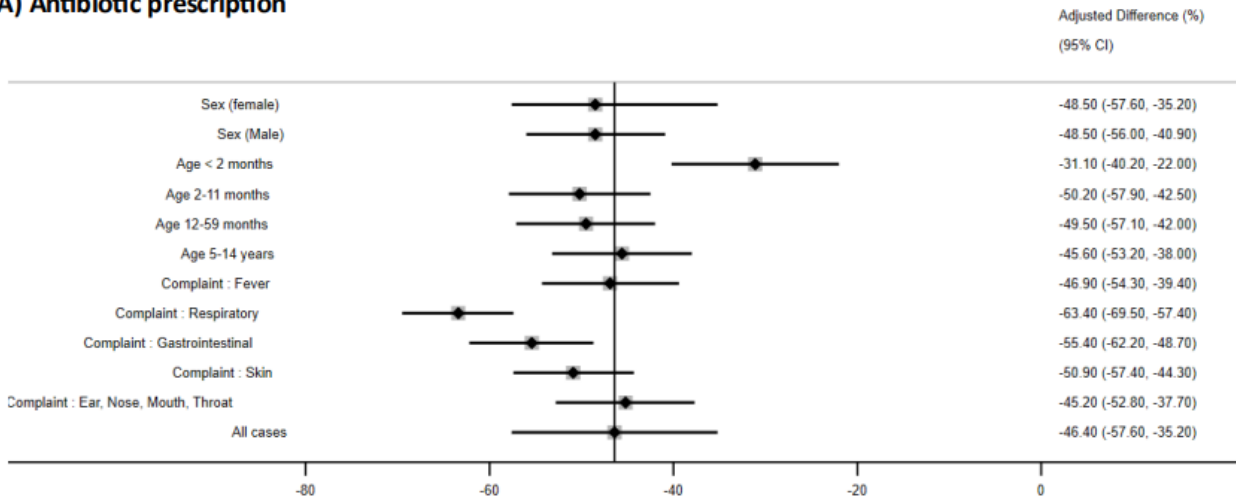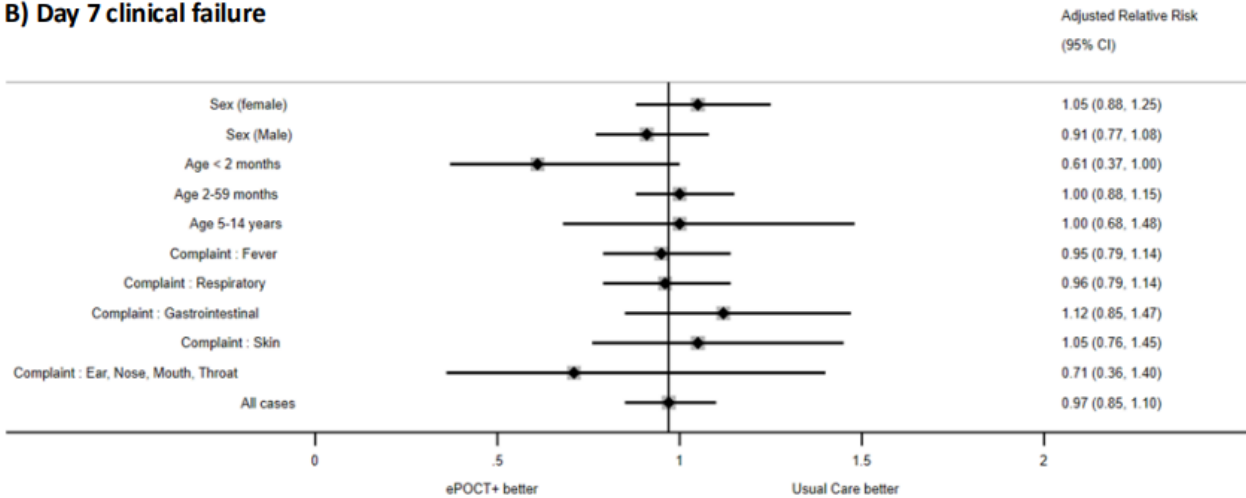|	Adjusted Difference (%) (95% CI)
Sex (female)	-48.50 (-57.60, -35.20)
Sex (Male)	-48.50 (-56.00, -40.90)
Age < 2 months	-31.10 (-40.20, -22.00)
Age 2-11 months	-50.20 (-57.90, -42.50)
Age 12-59 months	-49.50 (-57.10, -42.00)
Age 5-14 years	-45.60 (-53.20, -38.00)
Complaint : Fever	-46.90 (-54.30, -39.40)
Complaint : Respiratory	-63.40 (-69.50, -57.40)
Complaint : Gastrointestinal	-55.40 (-62.20, -48.70)
Complaint : Skin	-50.90 (-57.40, -44.30)
Complaint : Ear, Nose, Mouth, Throat	-45.20 (-52.80, -37.70)
All cases	-46.40 (-57.60, -35.20)

B) Day 7 clinical failure

	Adjusted Relative Risk (95% CI)
Sex (female)	1.05 (0.88, 1.25)
Sex (Male)	0.91 (0.77, 1.08)
Age < 2 months	0.61 (0.37, 1.00)
Age 2-59 months	1.00 (0.88, 1.15)
Age 5-14 years	1.00 (0.68, 1.48)
Complaint : Fever	0.95 (0.79, 1.14)
Complaint : Respiratory	0.96 (0.79, 1.14)
Complaint : Gastrointestinal	1.12 (0.85, 1.47)
Complaint : Skin	1.05 (0.76, 1.45)
Complaint : Ear, Nose, Mouth, Throat	0.71 (0.36, 1.40)
All cases	0.97 (0.85, 1.10)

Figure 3

Antibiotic prescription and clinical failure by sex, age groups, and main complaints

A) Adjusted differences of day 0 antibiotic prescription between ePOCT+ health facilities and usual care health facilities. B) Aadjusted relative risk with 95% CI of clinical failure in ePOCT+ compared to usual care health facilities

ePOCT+ Intervention package

C-Reactive Protein & Hemoglobin point-of-care tests

Pulse Oximeter

ePOCT+ Clinical Decision Support Algorithm

Dashboard on quality of care indicators

Mentorship support

Both intervention and control

- **Equivalent IMCI training**
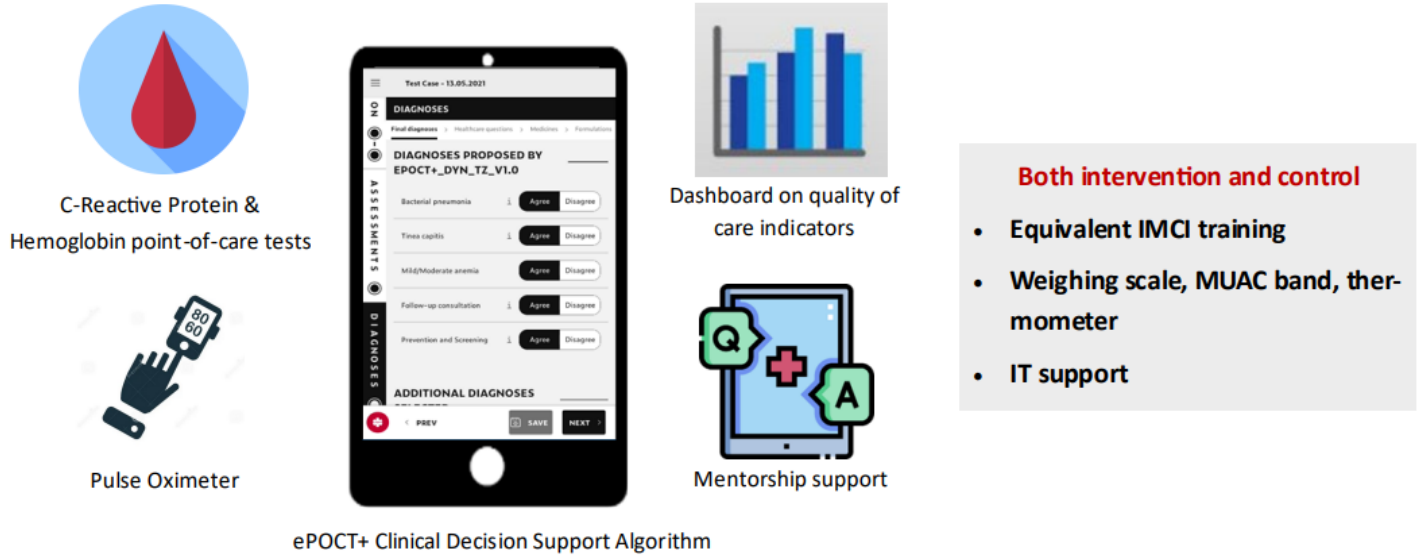- **Weighing scale, MUAC band, thermometer**
- **IT support**

Figure 4

Description of ePOCT+ and supportive mentorship intervention

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ePOCTClusterRCTSupplementarymaterial20230619.docx