Digital Clinical Support Tools to Improve Child Health:

Development, implementation, and evaluation of ePOCT+ to support healthcare providers in the management of sick children at primary care health facilities in Tanzania

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Summary

English:

Bacterial antimicrobial resistance due to inappropriate antibiotic use, and poor quality of care are major contributors to the unacceptably high childhood mortality in Tanzania. Electronic Clinical Decision Support Algorithms (CDSAs) are evidence based digital health tools based on clinical guidelines that guide health providers through a consultation to ultimately propose the diagnosis and treatment based on the inputs entered. Such tools have been found to reduce antibiotic prescription and improve quality of care. Nonetheless, there is a lack of pragmatic studies evaluating CDSAs in Tanzania, and there are many remaining challenges with previously developed CDSAs.

The aim of this project was to improve quality of care and reduce antibiotic prescription at primary care level health facilities in Tanzania. This was done by first developing the ePOCT+ clinical decision support algorithm, addressing challenges identified in other CDSAs, and secondly evaluating the effect of ePOCT+ on antibiotic prescription in a pragmatic cluster randomized controlled trial (DYNAMIC Tanzania study).

To improve uptake, adherence, safety, and potential for antibiotic stewardship, ePOCT+ expanded the clinical scope of the clinical algorithms, expanded the age range of patients it could manage, and assured comprehensive input from clinical and digital experts, as well as health provider end-users. Numerous meetings were conducted, Delphi processes were utilized, and comprehensive piloting was performed to develop ePOCT+. In order to assure safety, a systematic review was conducted to identify the best performing predictors of severe disease to integrate within the algorithm.

The DYNAMIC Tanzania study was a pragmatic, open-label, parallel-group, cluster randomized trial in 40 primary health facilities in the Mbeya and Morogoro regions of Tanzania. Randomization of health facilities were stratified by region, council, level of health facility, and attendance rate. The intervention consisted of the ePOCT+ CDSA with supporting IT infrastructure, C-reactive protein rapid test, hemoglobin rapid test, pulse oximeter, training and supportive mentorship. Co-primary outcomes were 1) antibiotic prescription at the time of the initial consultation (superiority analysis), and 2) clinical failure at day 7 defined as “not cured” and “not improved”, or unscheduled hospitalization (non-inferiority analysis). Secondary safety outcomes include unscheduled re-attendance visits, non-referred secondary hospitalization and death by day 7. Analyses were performed using a random effects logistic regression model using the cluster and patient as random effects, with further adjustment using fixed effect terms for randomization stratification factors, and baseline characteristics.

The systematic review on predictors of severe disease in febrile children presenting from the community identified 18 studies evaluating 200 prognostic factors and 25 clinical prediction models in 24 530 children. There were few outpatient and primary care studies identified. The most common and best preforming predictors of severe disease were malnutrition, altered consciousness, markers of acidosis, and poor peripheral perfusion.

In expanding the age scope of ePOCT+ to manage children 1 day to 15 years, and based on feedback from previous studies and CDSAs, additional illnesses were integrated in the ePOCT+ clinical algorithm. These include trauma, urinary tract infection, and abdominal pain, selected based on 1) incidence, 2) morbidity/mortality, and 3) feasibility at primary care. A Delphi survey among 30 Tanzanian health providers evaluated feasibility, acceptability and reliability of integrating specific predictors within ePOCT+, notably predictors identified within the systematic review. Feasibility tests in over 200 patients in 20 health facilities, and pilots in over 2000 consultations, lead to modifications to ePOCT+ based on user-experience feedback and observations, notably providing option to not measure some clinical signs when not feasible, allow health providers to accept or refuse a proposed diagnosis or treatment, provide alternative medicines in case of stock-outs, and highlighting clinical elements that would result in referral.

The DYNAMIC Tanzania cluster randomized trial took place between December 2021 to October 2022. Over 40,000 children under 15 years of age were enrolled in 20 health facilities (clusters) where health providers could use ePOCT+, and 20 health facilities where health providers provided care as usual. The co-primary outcomes found that the use of ePOCT+ resulted in a 3-fold reduction in the likelihood of a sick child receiving an antibiotic prescription compared to children in usual care health facilities. Despite substantially fewer antibiotics prescriptions, the co-primary outcome of clinical failure was non-inferior. There were also no differences in the secondary outcomes of death, secondary hospitalization, and additional medications after the initial consultations between study arms by day 7.

In conclusion, the ePOCT+ electronic clinical decision support algorithm if implemented to scale could help address the urgent problem of antimicrobial resistance by safely reducing antibiotic prescribing. Transfer of ownership to the ministry of health of Tanzania and integration within the Tanzanian digital health landscape will be essential in order to achieve wide scale implementation.

Kiswahili:

Usugu wa vimelea vya bakteria dhidi ya dawa za antibiotiki unaosababishwa na utumiaji usiofaa wa dawa, na huduma za matibabu zisizo bora ni sababu kubwa zinazochangia vifo vya watoto visivyokubalika nchini Tanzania. Algorithms ya Uamuzi wa Kliniki ya Elektroniki (CDSAS) ni zana za afya za kidigitali zenye miongozo ya matibabu ambayo inaongoza watoa huduma wakati wa mahojiano ya matibabu ili kupendekeza utambuzi wa ugonjwa na matibabu kulingana na taarifa zilizoingizwa. Zana kama hizi zimeonesha kupunguza matumizi ya dawa za antibiotiki na kuboresha ubora wa matibabu. Walakini, kuna ukosefu wa tafiti za kipragmatiki zinazotathmini CDSAs nchini Tanzania, na changamoto nyingi zilizoainishwa na CDSA za zamani.

Kusudi la mradi huu lilikuwa kuboresha huduma za matibabu na kupunguza matumizi ya dawa za antibiotiki katika vituo vya afya vya msingi nchini Tanzania. Hii ilifanyika kwanza kwa kuunda ePOCT+, muongozo unaosaidia kufanya maamuzi ya kimatibabu, kushughulikia changamoto zilizoainishwa katika CDSAs zingine, na pili kutathmini ufanisi wa ePOCT+ juu ya matumizi ya dawa za antibiotiki katika jaribio la kisayansi(Dynamic Tanzania).

Ili kuboresha uchukuliwaji, ufuatiliaji, usalama, na matumizi sahihi ya antibiotiki , ePOCT+ ilipanuawigo wa miongozo ya matibabu, ikaongeza umri wa wagonjwa inayoweza kutibu, na kuhakikisha inapokea mrejesho kutoka kwa wataalamu wa afya na kidigitalina vile vile watoa huduma wa afya ambao ni watumiaji wa mwisho. Mikutano mingi ilifanywa, michakato ya Delphi ilitumiwa, na majaribio kamili yalifanywa ili kuunda ePOCT+. Ili kuhakikisha usalama, mapitio ya machapisho za kisayansi yalifanyika ili kubaini viashiria vya magonjwa hatari na kujumuisha ndani ya muongozo.

Utafiti wa DYNAMIC Tanzania ulikuwa ni jaribio la kisayansi katika vituo 40 vya afya ya msingi nchini Tanzania. Uboreshaji wa vituo vya afya ulifanyika kulingana na mkoa, halmashauri, aina ya kituo cha afya, na kiwango cha mahudhurio. utafiti ulihusisha ePOCT+ CDSA ikisaidiwa na miundombinu za kitehama, kipimo cha haraka cha C-reactive protein, kipimo cha haraka wa wingi wa damu, kipima oksijeni,mafunzo na usimamizi elekezi. Matokeo ya msingi yalikuwa 1) matumizi ya dawa za antibiotiki wakati wa hudhurio la awali la matibabu (uchambuzi wa ukuu), na 2) kufeli kwa matibabu siku ya 7 kunakotafsirika kama "kutokupona" na "kutokupata nafuu", au kulazwa pasipo kuratibiwa (uchambuzi usio wa udhalili) . Matokeo ya pili ya usalamani pamoja na mahudhurio ya marudio yasiyoratibiwa, kulazwa hospitalini na kifo kwa siku ya 7. Uchanganuzi ulifanywa kwa kutumia muundo wa random effect logistic regression kwa kutumia nguzo na mgonjwa kama athari za bahati nasibu, na marekebisho zaidi kwa kutumia masharti ya athari ya kubadilika kwa ubinafsishaji mambo, na sifa za msingi.

Mapitio ya machapisho ya kisayansi juu ya viashiria vya magonjwa hatari kwa watoto wenye homa kutoka kwa jamii yaligundua machapisho 18 yenye kutathmini viashiria 200 vya maendeleo na mifano 25 ya utabiri wa kliniki katika watoto 24 530. Kulikuwa na machapisho machache juu ya kliniki za nje na huduma za afya ya msingi yaliyotambuliwa. Viashiria vya kawaida na vyenye ubora wa kuashiria ugonjwa wa hatari vilikuwa niutapiamlo, kupoteza fahamu, alama za acidosis, na mzunguko duni wa damu.

Katika kupanua wigo wa umri wa ePOCT+ kuhudumia watoto wa siku 1 hadi miaka 15, na kwa kuzingatia maoni kutoka tafiti za zamani na CDSAs, magonjwa ya ziada yalijumuishwa katika muongozo wa matibabu wa EPOCT+. Hii ni pamoja na majeraha, maambukizi ya njia ya mkojo, na maumivu ya tumbo, iliyochaguliwa kulingana na 1) visa vipya, 2) hali mbaya/vifo, na 3) uwezekano katika vituo vya afya vya msingi. Utafiti wa Delphi kati ya watoa huduma wa afya 30 wa Tanzania ulitathmini uwezekano, kukubalika na kutegemewa kwa kujumuishwa viashiria maalum ndani ya EPOCT+, hasa viashiria vilivyobainiwa ndani ya mapitio ya machapisho ya kisayansi. Vipimo vya uwezekano katika wagonjwa zaidi ya 200 katika vituo 20 vya afya, na majaribio katika mahojiano ya kimatibabu zaidi ya 2000, ulipelekea marekebisho ya EPOCT+ kulingana na maoni ya kiuzoefu na uchunguzi wa watumiaji, haswa kutoa chaguo la kutopima ishara kadhaa za ugonjwa wakati haiwezekani, kuruhusu watoa huduma wa afya kukubali au kukataa utambuzi wa ugonjwa au matibabu yaliyopendekezwa, kutoa dawa mbadala wakati wa kuishiwa kwa stoku, na kuainisha kwa vipengele vinavyoweza kupelekea rufaa.

Jaribio la DYNAMIC Tanzania lilifanyika kati ya Desemba 2021 hadi Oktoba 2022 katika mikoa ya Mbeya na Morogoro Tanzania. Zaidi ya watoto 40,000 chini ya umri wa miaka 15 waliandikishwa katika vituo 20 vya afya (vikundi) ambapo watoa huduma wa afya waliweza kutumia ePOCT+, na vituo 20 vya afya ambapo watoa huduma za afya walitoa huduma kama kawaida. Matokeo ya msingi yaligundua kuwa matumizi ya ePOCT+ yalisababisha kupungua mara 3 kwa uwezekano wa mtoto mgonjwa kupokea dawa ya antibiotiki ikilinganishwa na watoto katika vituo vya afya vya. Licha ya matumizi machache ya dawa za antibiotiki, matokeo ya msingi ya kufeli kwa matibabu hayakuwa duni. Hakukuwa na tofauti yoyote katika matokeo ya pili juu ya kifo, kulazwa hospitalini, na dawa za ziada baada ya mashauriano ya awali baina ya makundi ya kitafiti.

Kwa kuhitimisha, ePOCT+ muongozo wa kielektroniki wa kusaidia maamuzi ya matibabu ikiwa unatekelezwa kwa kiwango unaweza kusaidia kushughulikia shida ya haraka ya usugu wa antibiotiki l kwa kupunguza matumizi ya antibiotiki kiusalama. Uhamisho wa umiliki kwenda Wizara ya Afya ya Tanzania na ujumuishaji ndani ya mazingira ya afya ya kidigitali ya Tanzania itakuwa muhimu ili kufikia utekelezaji wa kiwango kikubwa.

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1. Preface

1.1. Acknowledgments

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1.2. Abbreviations

AMR	Antimicrobial resistance
CDSA	Clinical Decision Support Algorithm
CRP	C-reactive protein
EMR	Electronic Medical Records
ePOCT+	Not an abbreviation, the name of the clinical algorithm
IMCI	Integrated Management of Childhood Illness
LMIC	Low- and middle-income countries
POCT	Point-of-care test
RCT	Randomized Controlled Trial
SMART	Standards-based, Machine-readable, Adaptive, Requirements-based, and Testable
UNICEF	United Nations Children's Fund
WHO	World Health Organization

2. Introduction

2.1. Challenges in quality of care for sick children in primary care level health facilities in low-resource settings

Since 1990 there has been a 59% decrease in global childhood mortality rates, in part due to health interventions driven by the introduction of the Millennium Development Goals (Sharrow et al, 2022). Nonetheless, millions of children die from preventable or treatable causes every year, with the highest concentration occurring in Sub-Saharan Africa (Sharrow et al, 2022; UN IGME, 2023). Much of these preventable or treatable causes of death due to poor quality health services (Kruk et al, 2018a).

Quality health services is defined by the World Health Organization (WHO) as being effective, safe, people-centered, timely, equitable, integrated and efficient (World Health Organization, 2018a). Achieving this requires well-trained and sufficient healthcare providers. Staff shortages in primary care health facilities in low- and middle- income countries (LMIC) is all too common (Anyangwe & Mtonga, 2007; Willcox et al, 2015; World Health Organization, 2016a). The lack of medical doctors has resulted in the reliance on non-physician clinicians and community health workers at primary care level health facilities (Mullan & Frehywot, 2007; The Lancet Global, 2017; World Health Organization, 2016a). These health providers generally follow a 2-3 year program, receive very limited post-graduate training and infrequent supervision compared to the 5 year training and ongoing post-graduate training and supervision of medical doctors (Mullan & Frehywot, 2007). Despite this, many healthcare providers at primary care health facilities in Sub-Saharan Africa often demonstrate dedication and compassion for their patients, filling an important role in health services around the globe. Furthermore, the task-shifting of work traditionally done by medical doctors to non-physician clinicians or community health workers has been vital to the success of tackling HIV and reducing childhood mortality, and can often achieve similar or equivalent patient outcomes as compared to medical doctors (Emdin et al, 2013; Eyal et al, 2015; Mullan & Frehywot, 2007). Nonetheless there remains critical clinical knowledge gaps for which clinical guidelines, further training, supervision and mentoring could help address (Di Giorgio et al, 2020; Murphy et al, 2019).

Another challenge to achieving quality care health services in primary care health facilities in LMICs include the limited number of diagnostic tests available (Fleming et al, 2021). Diagnostic tests are essential for the diagnosis of specific diseases, distinguishing severity, prognostication, and

guiding treatment, and often perform better than clinical signs alone (Fleming et al, 2021; Keitel, 2019; Keitel et al, 2019a). These challenges complicated by the often limited resources available, may explain the poor quality of health services found in many low- and middle- income countries (Das et al, 2008; Di Giorgio et al, 2020; Kruk et al, 2017; Kruk & Freedman, 2008; Kruk et al, 2018b; Macarayan et al, 2018; van de Maat et al, 2021). Consequently, this contributes to millions of preventable deaths in children (Kruk et al, 2018a).

The Integrated Management of Childhood Illnesses (IMCI) chart book was introduced in the 1990s by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to address high childhood mortality and poor quality of care (World Health Organization, 2014). IMCI has been implemented in over 100 countries, found to likely improve quality of care, and may reduce mortality (Gera et al, 2016). Notwithstanding, poor adherence to IMCI protocols is common, consequently limiting its effectiveness (Kiplagat et al, 2014; Krüger et al, 2017; Lange et al, 2014). Among a myriad of causes, "cognitive overload", lack of motivation, and poor remunerations are important factors (Lange et al, 2014). Consequently, the introduction of guidelines, provision of printed material, and training without ongoing support has been found to have little to no effect on quality of care (Oxman et al, 1995). Evidence on methods to improve the implementation of IMCI by addressing issues in regards to poor adherence, and need of ongoing support is required.

While better implementation and adherence to IMCI can improve quality of care, there are still a number of clinical limitations to the guidelines. One major clinical limitation involves the identification of sick children in most need of a referral at primary care level health facilities (Buntinx et al, 2011). Identifying clinical signs, symptoms or tests that accurately predict which child is at risk of severe disease can help reduce morbidity/mortality of sick children and reduce misallocation of limited health care resources (Chandna et al, 2021a; McDonald et al, 2018; Molyneux et al, 2006).

Work from this PhD thesis addresses the challenges of poor quality of care in primary care health facilities in LMIC in a number of ways:

1) In chapter 3.1 we performed a systematic review to identify predictors and models that identify febrile children from the community that are at highest risk of developing a severe disease (manuscript published in BMJ Global Health, shared first author),

2) In chapter 3.2 we describe the development of the ePOCT+ clinical algorithm (manuscript published in PLOS Digital Health, first author) for which we:

a) Analyzed the predictors of severe disease from two previous clinical decision support algorithms (ePOCT and ALMANACH),

b) Performed a delphi survey on the appropriateness of specific clinical predictors for implementation at primary care, and

c) Evaluated how predictors of severe disease can be integrated in clinical algorithms, including the integration of clinical gestalt.

2.2. Challenges of bacterial antimicrobial resistance at primary care level health facilities in low-resource settings

Antibiotic prescription is inappropriately high in outpatient primary care settings in low- and middle- income countries (LMICs) (Chem et al, 2018; Fink et al, 2020; Gasson et al, 2018; Khalfan et al, 2021; Levine et al, 2022; Sulis et al, 2020), as well as in high-income countries (Durkin et al, 2018; Shively et al, 2018; van de Maat et al, 2019). Most recently a meta-analysis found that antibiotic prescription in LMICs occurs in 52% of consultations at primary care facilities (Sulis et al, 2020). High rates of antibiotic prescriptions have progressively increased over the last decade, and is projected to continue to increase over the next years (Klein et al, 2018; Van Boeckel et al, 2014). Inappropriate antibiotic prescription is one of the biggest contributors to the development of bacterial antimicrobial resistance (AMR) (Franco et al, 2009; Holmes et al, 2016; Rogues et al, 2007). Consequently, bacterial AMR is responsible for over 1.2 million deaths a year, as much as malaria and HIV combined (Murray et al, 2022). As such, AMR has been declared by the World Health Organization (WHO) as 'one of the biggest threats to global health, food security and development today' (World Health Organization, 2020). As AMR continues to rise and spread globally, antibiotic stewardship interventions are urgently needed (Laxminarayan et al, 2013; O'Neill, 2014).

With over 80% of antibiotic prescription occurring at primary care (Duffy et al, 2018; Suda et al, 2013; Wise et al, 1998), the need for antibiotic stewardship programs at the community level is especially important (Blanchette et al, 2018). Reducing antibiotic prescription at the community level has been found to be more effective in terms of reduction in bacterial AMR compared to the same proportion of antibiotic prescription reduction at the hospital level (MacFadden et al, 2019). The factors driving antibiotic prescription include the lack of awareness on the problems related to AMR by patients and healthcare providers, perceived and communicated pressure by patients and caregivers on health providers to prescribe antibiotics, economic incentives, fear of poor clinical outcomes, inappropriate peer norms and poor modelling by seniors (Eibs et al, 2020; Emgård et al, 2021; Radyowijati & Haak, 2003). In addition diagnostic and prescribing uncertainty, driven by the lack of available diagnostic tools, poor adherence to guidelines, and limited training and supervision,

are other important factors driving antibiotic prescription (Lopez-Vazquez et al, 2012; Md Rezal et al, 2015; Teixeira Rodrigues et al, 2013; Tonkin-Crine et al, 2017).

Antibiotic stewardship programs tend to be concentrated at the hospital level, nonetheless there is a growing call for more community based programs which are growing in numbers every year (Delory, 2022; Donà et al, 2020; Drekonja et al, 2015). One fundamental framework to reduce antibiotic prescription involves helping health providers distinguish whether their patient has bacterial versus viral illness. Clinical guidelines can help achieve this goal by providing clear guidance, protocols or algorithms to help distinguish whether the patient requires antibiotics. However, clinical guidance based on clinical signs alone is often insufficient to be able to accurately distinguish bacterial from viral illnesses. A recent analysis using the biggest and most geographically diverse childhood pneumonia dataset found that clinical signs and symptoms were poor predictors of radiographic pneumonia, an often used proxy for distinguishing bacterial pneumonia (Rees et al, 2020). The help of inflammatory marker diagnostic tests, can help. An evaluation of prediction rules and guidelines in detecting serious bacterial infections among Tanzanian febrile children, found that the integration of diagnostic tests within these prediction rules performed better than prediction rules that relied on clinical signs alone (Keitel et al, 2019a). C-reactive protein (CRP) and procalcitonin are the most common and researched diagnostic tests used to distinguish bacterial versus viral illnesses. Due to the availability of low-cost point of care CRP tests, and performing as well, if not better than procalcitonin (Erdman et al, 2015; Lubell et al, 2015), CRP has been the point of care diagnostic tests most often researched in low- and middle- income countries. A number of meta-analyses have found that CRP likely reduces antibiotic prescription, does not reduce clinical recovery, nor does it increase death or hospitalization, and no difference in patient satisfaction (Smedemark et al, 2022; Verbakel et al, 2019) . A closer look at the biggest randomized trials evaluating CRP finds similar problems: low uptake of CRP test use, low adherence to CRP results, high variability in prescribing, and ultimately high absolute proportion of patients receiving antibiotics and only a small reduction compared to control arm (Althaus et al, 2019; Do et al, 2016; Do et al, 2023). Another major issue plaguing many of these studies, surrounds the lack of guidance on which patients should be tested, resulting in a high number of patients with low pre-test probability of a bacterial illness being tested, and as such a risk of false positives, and unclear threshold to use to guide health providers (Keitel, 2019). Better selection of patients to be tested with CRP integrated within clinical guidance via digital tools may help address this issue. Indeed success of different antibiotic stewardship interventions are variable, with acknowledgment that multi-faceted interventions addressing many factors driving antibiotic prescription are often more successful (Cox et al, 2017; Zay Ya et al, 2023).

Work from this PhD thesis addresses the challenges of high antibiotic prescription in primary care health facilities in LMIC in two sections:

a) Evaluating methods to improve antibiotic stewardship in the design of ePOCT+ by notably including point-of-care tests (POCT) such as C-Reactive Protein (CRP) in chapter 3.2 (published manuscript in PLOS Digital Health, first author).
b) Evaluating the impact of using ePOCT+ in primary care health facilities in a cluster randomized controlled trial (published manuscript in Nature Medicine, first author)

2.3. Digital clinical support tools to improve care in primary care level health facilities

With the rapid expansion of digital technology, there is rising enthusiasm for leveraging digital health to enhance healthcare systems (World Health Organization, 2018b). Clinical decision support system (CDSS) are digital tools that present recommendations to users based on patient-specific information, ranging from simple information alerts in an electronic medical record system, to complex and comprehensive decision support (Musen et al, 2021). Clinical decision support algorithms (CDSAs) are categorized as a subtype of CDSS', and the focus of digital health tools discussed in this thesis. These tools are usually tablet-based or mobile health applications that comprehensively guide healthcare workers through the whole consultation, prompting them on what symptoms, signs and tests to assess in order to propose the appropriate diagnosis and treatment (Keitel & D'Acremont, 2018; Pellé et al, 2020). Such tools are among the 28 groups of digital health interventions outlined by WHO showing promise for improving quality of care (World Health Organization, 2019).

CDSAs can improve quality of care at the primary care level in a number of ways. First, they help health providers to better adhere to clinical guidelines. This is done by guiding providers step-by-step through assessment of relevant symptoms and signs, and providing suggested diagnoses and treatments based on their responses. While some paper guidelines follow a step-by-step format, the digital version can integrate mandatory responses to ensure systematic assessment, which of course is not possible for paper guidelines. A number of studies have demonstrated improvements in guideline adherence by healthcare providers using CDSAs compared to paper guidelines. For example, in Tanzania healthcare providers assessed 70.9% of children for all ten essential clinical symptoms and signs when using a CDSA, compared to 20.7% of children when using paper guidelines ($p<0.001$) (Mitchell et al, 2013). Further studies in Tanzania, Afghanistan, Nigeria, and Burkina Faso

have shown similar benefits (Bernasconi et al, 2019; Bernasconi et al, 2018a; Rambaud-Althaus et al, 2017; Sarrassat et al, 2021).

Improved quality of care through the use of CDSAs has translated to improved clinical outcomes by a number of tools. First, clinical cure was found to be higher in health facilities using CDSAs compared to routine care in a number of trials in Tanzania and Nigeria (Keitel et al, 2017; Schmitz et al, 2022; Shao et al, 2015a). Second, some studies have found major reductions in antibiotic prescriptions through the use of CDSAs with similar or improved proportion of clinical cure (Keitel et al, 2017; Shao et al, 2015a). Third, patient/caregiver satisfaction may be improved, with for example some reporting to be especially happy that "[children were] touched by nurses much more often than before" due to increased physical examinations performed (Bessat et al, 2019). In addition qualitative studies with healthcare providers often found that the use of CDSAs improved knowledge and skills, and simplified work (Bessat et al, 2019; Finette et al, 2019; Jensen et al, 2020; Mitchell et al, 2012; Shao et al, 2015b). Finally, a cost-effectiveness study found positive results when evaluating the implementation of the IeDA CDSA in Burkina Faso (Cousens et al, 2018).

While there is much enthusiasm for the successful implementation of CDSAs, the impact remains heterogeneous. A recent study in South Africa found quality of care to be worse when using a CDSA compared to paper guidelines (Horwood et al, 2023), and a recent systematic review of CDSAs determined that evidence of improvements in quality of primary care was uncertain (Agarwal et al, 2021). In addition, a number of limitations of the CDSAs have been highlighted by health providers using CDSAs, notably the limited scope of diagnoses and patient age groups (Bessat et al, 2019; Jensen et al, 2020; Mitchell et al, 2012; Shao et al, 2015b), and IT challenges (Chirambo et al, 2021; Jensen et al, 2020; Shao et al, 2015b). Such limitations may explain in part difficulties with uptake of CDSAs (Jensen & McKerrow, 2022; Jensen et al, 2020; Shao et al, 2015b), and why some tools had little to no impact on antibiotic stewardship (Bernasconi et al, 2019; Horwood et al, 2023; Kapisi et al, 2023; Sarrassat et al, 2021; Schmitz et al, 2022). Furthermore to date a number of methodological issues renders the interpretation of results difficult, with many studies not randomized (Bernasconi et al, 2019; Bernasconi et al, 2018b; Mitchell et al, 2013; Schmitz et al, 2022; Shao et al, 2015a), and even fewer randomized trials in close-to real-world settings (Rambaud-Althaus et al, 2017; Sarrassat et al, 2021). To date, no cluster randomized trial has evaluated the impact of a CDSA powered for clinical outcomes (Agarwal et al, 2021; Keitel & D'Acremont, 2018).

Work from this PhD thesis addresses the gap in evidence of CDSAs in two sections:

c) Development of the ePOCT+ CDSA, and the medAL-suite app in chapter 3.2 (published manuscript in PLOS Digital Health, first author).

d) Evaluating the impact of using ePOCT+ in primary care health facilities in a cluster randomized controlled trial (in review at Nature Medicine, preprint on In Review platform, first author)

2.4. Setting: Tanzanian context

The majority of the work from this PhD was conducted in the United Republic of Tanzania, in Sub-Saharan Africa. In order to contextualize the three previous chapters from a Tanzanian perspective, the present section will briefly summarize pertinent demographic data, health system organization, evidence on quality of care, antibiotic use, antibiotic stewardship initiatives, and the use of digital health tools in Tanzania.

Demographic overview

Tanzania has a population of 61,741,120 people, doubling in size over the past two decades, comprising over 100 different tribes, with 65% living in rural areas (United Republic of Tanzania (URT), 2022). Children under 15 years comprise 42.8% of the total population (United Republic of Tanzania (URT), 2022). The Gross Domestic Product (GDP) at purchasing power parity (PPP) per capita of Tanzania was 3,600$, which ranks Tanzania 161th out of 192 countries (International Monetary Fund, 2023).

Healthcare system

The Tanzanian healthcare system is structured around a multi-tiered decentralized structure (table 1). Community care is provided by village health workers or community health workers directly at the homes of patients or at community health posts by village/community health workers with no formal health training. At the primary care level, care is provided at dispensaries by enrolled nurses (2 years training after secondary school), clinical assistants (2 year training after secondary school), or clinical officers (3 years training after secondary school, and in health centers where it is run with the same health providers as dispensaries with the rare addition of assistant medical officers (clinical officers with an additional 2 years of clinical training) or medical doctors (5 year training after secondary school) in some facilities (Kwesigabo et al, 2012).

Table 1: Tanzanian health system structure

Care level	Administrative level	Structure	Highest level health providers
Community Care	Village	- Homes	Village/Community Health Worker

		- Community Health Post	
Primary Care	Ward	Dispensary	Clinical Officer, Enrolled nurses
Primary Care	Divisions	Health Centre	Medical Doctor*, Assistant Medical Officers, Clinical Officers
Secondary Care	District	District Hospital	Medical Doctor, Assistant Medical Officers
Tertiary Care	Region	Regional Hospital	Specialist Medical Doctor
	Zone	Referral/Specialized Zonal Hospital	Specialist Medical Doctor
	National	Referral/Specialized National Hospital	Specialist Medical Doctor

*The presence of medical doctors at health centres is at present rare, most are staffed by clinical officers

In 2018, there were 0.5 medical doctors and 5.5 nursing and midwifery personnel per 10,000 population (World Health Organization, 2023), well below the minimum density of doctors, nurses, and midwives as defined by the WHO's "Sustainable Development Goal index threshold" of 44.5 per 10,000 population (World Health Organization, 2016b). Given this shortage, Tanzania has drastically increased the number of medical doctors it trains, however the number of postings available have not kept up, leaving many new medical doctor graduates without jobs (Goodell et al, 2016). Furthermore, despite government incentives to encourage doctors to work in rural areas, many recent graduates do not wish to work in rural areas, where the majority of Tanzanians live, resulting in inequitable and uneven geographical distribution of doctors (Goodell et al, 2016; Sirili et al, 2019). To compensate for this shortage, as described in chapter 2.1, non-physician clinicians such as clinical officers and assistant medical officers in Tanzania, take on the responsibilities of medical doctors in many primary care level health facilities.

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) (Amu et al, 2018).

Quality of Care and Health Outcomes

There are many successes due to longstanding efforts within the Tanzanian health care system to improve quality of care and improve health outcomes. Efforts to improve care seeking for ill children in Tanzania has lead to 79% of children with symptoms of acute respiratory illnesses, and 78% of

children with fever to seek care within the Tanzanian Health System (Ministry of Health (MoH) Tanzania Mainland et al, 2023). Over the past 2.5 decades, Tanzania has seen incredible progress in health outcomes, with notably a more than a 3-fold reduction in under-5 mortality, a 2-fold increase in the percentage of women receiving antenatal care from a skilled provider for their last live birth (currently 85%), a 2-fold increase in the proportion of children age 0-5 months being exclusively breastfed, and a 1.5 fold reduction in the proportion of children under age 5 years who are stunted (short for their age) (Ministry of Health (MoH) Tanzania Mainland et al, 2023). In addition over the last 15 years, malaria prevention programs, notably the distribution of insecticide-treated bednets, have driven a 2-fold reduction in the proportion of febrile children age 6-59 months testing positive for malaria (currently 8%) (Ministry of Health (MoH) Tanzania Mainland et al, 2023).

Nonetheless, the under-5 mortality of 43 deaths per 1,000 live births, infant mortality of 33 deaths/1,000 live births, and neonatal mortality of 24 deaths/1,000 live births remains unacceptably high (Ministry of Health (MoH) Tanzania Mainland et al, 2023). Unsatisfactory quality of care, and overall low performance of health service delivery may be partly to blame. Common problems include:

- Insufficient health workers, and poor morale (Afnan-Holmes et al, 2015; Kwesigabo et al, 2012; Mamdani & Bangser, 2004)
- Poor adherence to clinical guidelines (Kiplagat et al, 2014; Krüger et al, 2017; van de Maat et al, 2021; Walter et al, 2009)
- Lack of clinical examinations by health providers (Kahabuka et al, 2012)
- Little to no supervision and mentorship of health workers (Kwesigabo et al, 2012; Manzi et al, 2012; Renggli et al, 2019)
- Lack of essential drugs (Kahabuka et al, 2012; Ministry of Health and Social Welfare, 2007)
- Lack of equipment and medical supplies (Kahabuka et al, 2012; Kwesigabo et al, 2012)
- Problems with hygiene, notably a lack of safe and continuous water supplies in some health facilities (Kahabuka et al, 2012)

Addressing these problems has been the priority for the Ministry of Health and other stakeholders (Gage et al, 2020; Yahya & Mohamed, 2018), and part of the overall goal of this PhD.

Antibiotic use and antibiotic stewardship

As found around the world, and especially in low- and middle- income countries, excessive antibiotic use is common in Tanzania (Fink et al, 2020; Keitel et al, 2017; Levine et al, 2022; van de Maat et al, 2021), and increasing (Mbwasi et al, 2020; Sangeda et al, 2021). In response, the Tanzanian

government released Tanzania's National Action Plan on AMR, describing the strategy for surveillance of antibiotic use and AMR, and outlining how to reduce AMR, by notably decreasing human and animal antibiotic use (United Republic of Tanzania Ministry of Health Commmunity Development Gender elderly and children, 2017). While this action plan has already resulted in several achievements (development of coordination committees, governance structures, surveillance structures, awareness campaigns, and guidelines), there remains much work to be done and numerous challenges to overcome (Frumence et al, 2021).

Digital health

Tanzania is seen as a leader in the digital health world (Watts, 2020), with over 160 digital health or health-related systems (Tanzania Ministry of Health, 2019). Recognizing the potential of such digital tools, the Tanzanian government developed important guidance on the investment road map of digital health (Government of Tanzania, 2017), and the Tanzanian digital health strategy (Tanzania Ministry of Health, 2019). The latter was developed with the goal of "accelerating increased access to and improved quality of effective and efficient health care to all Tanzanians through digitally enabled transformation of the health system" (Tanzania Ministry of Health, 2019). The digital health tools implemented in Tanzania are wide ranging, from electronic health records systems (Hamad, 2019), data collection tools for supported supervision (Renggli et al, 2018), disease surveillance systems (Mustafa et al, 2023), e-learning tools (Meaney et al, 2023), guideline based CDSAs (Beynon et al, 2023; Keitel & D'Acremont, 2018), and artificial intelligence-based innovations (Sukums et al, 2023).

More specifically, some of the first electronic clinical decision support algorithms were developed in Tanzania, notably eIMCI (Mitchell et al, 2012; Mitchell et al, 2013), ALMANACH (Rambaud-Althaus et al, 2015; Shao et al, 2015a), and ePOCT (Keitel et al, 2017). However the three aforementioned CDSAs were never truly implemented in routine settings, and health providers have called for expanded content within the algorithms to include other pathologies and age-groups (Shao et al, 2015b).

2.5. Rationale for PhD thesis

Within this introduction we have seen the potential benefit of electronic clinical decision support algorithms to address the problems of quality of care and inappropriate antibiotic use in primary care health facilities in Tanzania. The lack of pragmatic, real world studies on the use of CDSAs

implemented in Tanzania, the limited scope and challenges with previous CDSAs were the primary reasons for the topic of this PhD thesis.

3. Goals and Objectives

3.1. Research questions

- What clinical symptoms, signs, or tests can be used to identify which febrile child will develop a severe illness?
- How to develop and implement a digital clinical decision support algorithm?
- Will health providers use and adhere to a digital clinical decision support algorithm implemented in a close to real-world setting?
- Will health providers follow treatment recommendations of a clinical decision support algorithm implemented in close to real-world setting, and thus reduce overall antibiotic prescription? Will such a reduction of antibiotic prescription be safe?

3.2. Goal

To improve quality of care and reduce antibiotic prescription in the management of sick children less than 15 years old using digital clinical decision support algorithms at primary care level health facilities in Tanzania.

3.3. Objectives

- To identify the best predictors and models of severe disease in febrile children presenting to care
- To develop ePOCT+, a digital clinical decision support algorithm (CDSA), for the management of sick children less than 15 years old at primary care level health facilities in Tanzania.
- To evaluate the impact of ePOCT+ compared to usual care on antibiotic prescription and clinical outcome of sick children less than 15 years old visiting a primary care level health facilities in Tanzania

4. Methodological overview

This PhD was divided in two steps, the first surrounded the development of the ePOCT+ clinical decision support algorithm, and step two the evaluation of ePOCT+ in a cluster-randomized controlled trial.

4.1. Step 1: Development of ePOCT+

The first step of developing ePOCT+ was divided in two subprojects. First, we performed a systematic review on predictors of severe disease in febrile children, and secondly, integrating the findings of this systematic review and other findings to develop ePOCT+.

Systematic review on predictors of severe disease in febrile children:

The systematic review included prognostic studies including children aged >28 days and <19 years presenting from the community with an acute febrile illness. Studies that did not have disaggregated pediatric data, only included patients with a specific syndrome or illness, or enrolled less than 20 patients were excluded. The primary outcome was any objective measure of disease severity within 30 days of measurement of the predictors or during hospitalization. The search was restricted to MEDLINE, Embase and Web of Science databases, without language restrictions, and limiting to studies between 31 May 2019 to 30 April 2020. All title, abstract, and full-text screening were performed by two reviewers, data was extracted by one reviewer and reviewed by another, and risk of bias and applicability was evaluated by three reviewers. Prognostic factors were compared using the positive likelihood ratio, and negative likelihood ratio, while clinical prediction models were compared using the area under the receiver operating characteristic curve.

Development of ePOCT+:

Numerous processes were undertaken to develop ePOCT+:

Scope: Demographic scope in terms of age was determined based on the clinical relevance of having a single algorithm for all pediatric patients, and considering the high morbidity/mortality of young infants less than 2 months old. The scope of clinical syndromes and illnesses, were evaluated based on three major criteria: 1)incidence of presenting symptoms and diagnoses at primary care health facilities in Tanzania; 2) Morbidity, mortality, and outbreak potential; and 3) Capacity to diagnose and manage at the primary care level health facilities. In addition conditions included in IMCI and national clinical guidelines were considered.

Clinical algorithm and digital adaptation:

a) Feasibility, acceptability, and reliability of predictors: To assure optimal utilization, each symptom, sign and test included in the algorithm must be feasible, acceptable, and reliably assessed by health providers. To assess this we performed a Delphi survey among 30 Tanzanian health care workers and conducted feasibility tests using a preliminary versions of ePOCT+ on real and fictional cases, observing use, and collecting feedback.
b) Diagnostic and prognostic value of predictors: Results from the systematic review described previously, as well as an exploratory analysis on the prognostic value of predictors integrated in two previous generation clinical decision support algorithms were analyzed. These findings, in addition to other previous work(De Santis et al, 2017; Keitel et al, 2019b; Tan et al, 2020), were integrated into ePOCT+ to assure safety.
c) Decision logic: was then developed based on IMCI and national clinical guidelines, the previous methods described, and integrating overall clinical impression when possible. Sensitivity and specificity of algorithm branches were considered in relation to severity and pre-test probability of conditions to assure safety for severe conditions, limiting antibiotics for less severe illnesses, and limiting misallocation of limited health care resources
d) Expert review: all clinical algorithms were reviewed and approved by an international panel of digital health experts, and clinical experts from each country of implementation.

Validation tests and piloting:

Validation tests were conducted for each diagnosis to ensure that inputted data resulted in the expected result. In addition desk-based user interface tests were conducted to assess user interface. Finally ePOCT+ was piloted in over 2000 consultations, with adaptations based on feedback occurring at various steps along the way.

4.2. Step 2: Evaluation of ePOCT+ in a cluster-randomized controlled trial

Study design: Pragmatic, open-label, parallel-group cluster randomized trial.

Setting: 5 councils (two semi-urban, and three rural) in the Mbeya and Morogoro region including areas with high and low malaria prevalence.

Cluster inclusion criteria: Primary care health facilities (dispensaries or health centers) performing 20 or more consultations per week of children 2 to 59 months, were government or government designated health facilities, and located less than 150km from the two research institutions located in Mbeya city and Ifakara town.

Patient inclusion criteria: Infants and children aged 1 day old to less than 15 years of age seeking care for an acute medical or surgical condition at participating health facilities.

Randomization: Health facilities were randomized 1:1 stratified by region, council, level of health facility (health center versus dispensary), and attendance rate. Computer-generated randomization was performed by an independent statistician.

Intervention: ePOCT+ clinical decision support algorithm, with supporting IT infrastructure, C-reactive protein lateral flow test, hemoglobin point-of-care test, pulse oximeter, training and supportive mentorship.

Study procedures: Screening and enrollment was conducted by research assistants on workdays at health facilities. Health providers entered data on presenting complaints, final diagnosis, treatment, and referral status. 7 days after a patient visit, research assistants called the caregivers of patients to assess if the child is cured, improved, the same, worse, hospitalized or dead, and assessed whether other medications not prescribed on day 0 were taken.

Outcomes: The co-primary outcome measures were 1) antibiotic prescription at the time of the initial consultation (superiority analysis), and 2) Clinical failure ("not cured" and "not improved", or unscheduled hospitalization) at day 7 (non-inferiority analysis). Secondary safety outcomes include unscheduled re-attendance visits, non-referred secondary hospitalization, and death by day 7.

Sample size: Sample size was based on the co-primary outcome of non-inferiority of clinical failure (requires higher sample size). Assuming a cluster size of 900 patients per health facility over 6 months, an intraclass correlation coefficient of 0.002, and a clinical failure rate of 3%, we would have 80% power to detect an acceptable non-inferiority margin of a relative risk of 1.3%, with 19 clusters per arm. Given the uncertainty of some of the assumptions, the total number of health facilities was rounded up to 20 clusters per arm.

Statistical analysis: A random effects logistic regression model using the cluster and patient as random effects was used. Further adjustment using fixed effect terms were used including randomization stratification factors, and baseline characteristics hypothesized to be associated with the outcome, imbalances between arms, and imbalances between characteristics among patients fro who day 7 data was available and not available.

5. Publications

5.1. Predictors of severity in febrile children attending primary care health facilities: a systematic review of prognostic studies

Title	Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies
Full author list	Arjun Chandna*, **Rainer Tan*,** Michael Carter, Ann Van Den Bruel, Jan Verbakel, Constantinos Koshiaris, Nahya Salim, Yoel Lubell, Paul Turner**, Kristina Keitel** ***Contributed equally – shared first authorship** **Contributed equally – shared last authorship
Journal	BMJ Global Health
Date of publication	20 January 2021
Doi:	http://dx.doi.org/10.1136/bmjgh-2020-003451
Supplementary material / annexes	https://gh.bmj.com/content/bmjgh/6/1/e003451.full.pdf?with-ds=yes
RT contribution	Developed study design; Defined the review strategy; Conducted the search, screened retrieved articles and extracted the data; Assessed quality of included articles; Analyzed the data and drafted the report. Specific division of tasks between the two shared first authorship authors: RT: Led all aspects related to the clinical prediction models: data analysis and writing sections of the manuscript on the clinical prediction models AC: Led all aspects related to the individual prognostic factors: data analysis and writing sections of the manuscript on the individual prognostic factors The rest of the work was done equally between both first authors.

BMJ Global Health

Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies

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ABSTRACT

Introduction Early identification of children at risk of severe febrile illness can optimise referral, admission and treatment decisions, particularly in resource-limited settings. We aimed to identify prognostic clinical and laboratory factors that predict progression to severe disease in febrile children presenting from the community.

Methods We systematically reviewed publications retrieved from MEDLINE, Web of Science and Embase between 31 May 1999 and 30 April 2020, supplemented by hand search of reference lists and consultation with an expert Technical Advisory Panel. Studies evaluating prognostic factors or clinical prediction models in children presenting from the community with febrile illnesses were eligible. The primary outcome was any objective measure of disease severity ascertained within 30 days of enrolment. We calculated unadjusted likelihood ratios (LRs) for comparison of prognostic factors, and compared clinical prediction models using the area under the receiver operating characteristic curves (AUROCs). Risk of bias and applicability of studies were assessed using the Prediction Model Risk of Bias Assessment Tool and the Quality In Prognosis Studies tool.

Results Of 5949 articles identified, 18 studies evaluating 200 prognostic factors and 25 clinical prediction models in 24 530 children were included. Heterogeneity between studies precluded formal meta-analysis. Malnutrition (positive LR range 1.56–11.13), hypoxia (2.10–8.11), altered consciousness (1.24–14.02), and markers of acidosis (1.36–7.71) and poor peripheral perfusion (1.78–17.38) were the most common predictors of severe disease. Clinical prediction model performance varied widely (AUROC range 0.49–0.97). Concerns regarding applicability were identified and most studies were at high risk of bias.

Conclusions Few studies address this important public health question. We identified prognostic factors from a wide range of geographic contexts that can help clinicians assess febrile children at risk of progressing to severe disease. Multicentre studies that include outpatients are required to explore generalisability and develop data-driven tools to support patient prioritisation and triage at the community level.

PROSPERO registration number CRD42019140542.

Key questions

What is already known?

- An increasing number of clinical decision-support algorithms and risk stratification tools integrate clinical and laboratory predictors to guide healthcare workers in their assessment of febrile children.
- Which prognostic factors—alone or as components of clinical prediction models—best identify children at risk of developing severe febrile illness is not clear.
- Previous systematic reviews have focused on diagnostic studies and used imperfect reference standards for severe disease.

What are the new findings?

- Malnutrition, hypoxia, altered consciousness, and bedside markers of acidosis and poor peripheral perfusion were the most commonly identified predictors of severe disease.
- Clinical prediction model performance varied—the best performing models being those evaluated in similar settings and using similar outcomes as the original derivation studies.
- The prognostic factors and clinical prediction models identified in this study reflect children with relatively advanced illnesses and hence the degree to which they can inform community triage and prioritisation strategies is unclear.

INTRODUCTION

Acute febrile illnesses are among the most common reasons that parents seek medical care for their children.[1 2] While most episodes are mild, an important minority of children progress to severe disease. Early recognition of low-incidence serious disease is challenging,[3] especially in many tropical settings where health workers receive limited training, patient volumes are high, diagnostic capacity is poor and different acute febrile syndromes are often clinically indistinguishable.[4 5]

Key questions

What do the new findings imply?

- The studies included in this systematic review, together with other studies, highlight the importance of not over interpreting prognostic performance of individual predictors, which vary across different epidemiological contexts.
- If prediction models and decision-support algorithms are to be used as an adjunct to clinical assessment, they must be derived and validated using populations and outcomes appropriate to the clinical problem.
- To improve identification of children at risk of developing severe febrile illness, this will require multiple, large, collaborative research initiatives, which collect harmonised yet contextualised data on predictors and outcomes, and include unselected children presenting from the community.

Clinical and laboratory prognostic factors that enable early and accurate identification of children at risk of developing severe disease could improve patient outcomes and reduce resource misallocation.[6 7] An increasing number of clinical decision-support algorithms and risk stratification tools integrate clinical and laboratory predictors to guide referral, admission and treatment decisions.[8] While no unified strategy exists to guide selection of candidate predictors, those already reported as prognostic should normally be considered.[9]

Previous reviews have evaluated predictors of 'serious bacterial infections'.[10 11] However, these studies are diagnostic rather than prognostic.[9] Furthermore, 'serious bacterial infection' is an imperfect measure of disease severity: microbiological tests for bacterial infections lack sensitivity, especially in settings with high antibiotic consumption; 'serious bacterial infections' are not always severe (eg, children with enteric fever are often successfully managed as outpatients) and severe febrile illnesses are frequently caused by non-bacterial pathogens, especially in low/middle-income countries (LMICs),[4 12] in part secondary to the introduction of widespread vaccination against prevalent bacterial pathogens of childhood.[13]

We performed a systematic review to identify which clinical and laboratory factors—alone or as part of clinical prediction models—predict progression to severe disease in febrile children presenting from the community to a community health worker, primary health centre or hospital outpatient or emergency department. Our aim was to understand which prognostic factors might support health workers faced with this difficult and common clinical question and to inform variable selection for future prospective studies aiming to develop data-driven triage tools.

METHODS

Protocol and registration

The methods for this systematic review were specified in advance (PROSPERO protocol: CRD42019140542) and adhere to the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS),[14] a modification of CHARMS for prognostic factor studies (CHARMS-PF),[15] Quality In Prognosis Studies (QUIPS)[16] and Prediction Model Risk of Bias Assessment Tool (PROBAST) guidelines.[17] The report has been prepared in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[18]

Eligibility criteria

All prognostic studies (prognostic factor and clinical prediction model) including ≥20 patients were eligible. Our target population was children aged >28 days and <19 years, presenting from the community with an acute febrile illness (documented abnormal temperature (fever or hypothermia) or history of fever) or suspected sepsis. While sepsis is not always well defined in children,[19] 'suspected sepsis' was included along with febrile children so as to include all children with suspected infection. Studies were excluded if disaggregated paediatric data were not presented or patients were recruited partway through receipt of inpatient treatment, as the aim of the review was to identify *prognostic* variables measured at presentation. Studies that only evaluated specific clinical syndromes (eg, neurological presentations, acute respiratory infections and so on) or particular pathogens (eg, *Plasmodium* spp, influenza and so on) were not included.

Studies measuring predictors at presentation to care were included. Studies where authors identified that a substantial proportion of participants were recruited following transfer from another health facility were excluded. Demographic, anthropometric, socioeconomic, clinical and historical variables were considered, as well as laboratory parameters measured at presentation to care. Studies only reporting variables that would not be available at the time of presentation to care (eg, blood culture results) were excluded.

The primary outcome was any objective measure of disease severity occurring within 30 days of measurement of the predictors or during hospitalisation. Studies assessing outcome at the same time point as baseline predictor measurements (diagnostic studies) were excluded.

Search strategy and selection criteria

We searched MEDLINE, Embase and Web of Science databases, without language restriction, for publications between 31 May 1999 and 30 April 2020 (initial search to 31 May 2019; updated search to 30 April 2020). We followed Cochrane Prognosis Methods Group recommendations to build our search strategy (online supplemental appendix S1), structured according to the 'populations, interventions, comparators, outcomes, timing and setting' (PICOTS) framework and adapted published search strings as appropriate.[20–22] The search

strategy was peer-reviewed by an independent Technical Advisory Panel (online supplemental appendix S2).

Study selection

Title, abstract and full-text screening were performed independently by two reviewers (AC and RT). Agreement was checked after the first 20 and 250 articles. Discrepancies were resolved by discussion or independent assessment by a third reviewer (KK).

Eligible studies and relevant review articles were 'snowballed' (forward and reverse crosschecking of reference lists) to identify additional studies. The list of eligible studies was presented to the Technical Advisory Panel who were asked to identify obvious omissions and suggest key authors whose publication lists were subsequently reviewed for additional eligible studies (online supplemental appendix S2).

Data collection process

Data extraction sheets were developed based on the CHARMS and CHARMS-PF checklists (online supplemental appendix S3).[14 15] Data were extracted independently by one reviewer (AC or RT) and checked by the other. Discrepancies were discussed and resolved between the two reviewers. Authors of studies not reporting likelihood ratios (LRs) (prognostic factors) or area under the receiver operating characteristic curves (AUROCs) (clinical prediction models), or the data to allow their calculation, were contacted. Seven authors responded to requests for clarifications and six provided additional data not available in the published manuscript. All predictors were harmonised using the Systematised Nomenclature of Medicine Clinical Terms (SNOMED-CT).

Data analysis: prognostic factors

Contingency tables were constructed and positive likelihood ratio (PLR) and negative likelihood ratio (NLR) calculated for each prognostic factor. In the case of an empty cell, 0.5 was added to each cell (Haldane-Anscombe correction). CIs were calculated on the basis of the SE of a proportion (Stata V.16.0). LRs were selected as the principal effect estimate as they allow estimation of post-test probabilities, are independent of prevalence, are intuitive for clinicians and are frequently used to compare performance of predictors in diagnostic and prognostic studies.[10 11 23 24] Prognostic factors are presented in the main analysis if at least one study reported a PLR ≥5.0 (ie, a rule-in test), or a NLR ≤0.2 (ie, a rule-out test).[23] To contextualise the results, we used the outcome prevalence of individual studies to calculate the pre-test probability, and display positive and negative post-test probabilities on dumbbell plots (R V.3.6.1).

Data analysis: clinical prediction models

For clinical prediction models, AUROCs are presented on forest plots (Stata V.16.0). When available, we present LRs for different thresholds of the models in online supplemental appendix S4.

Synthesis of results

Due to expected heterogeneity between studies (as a result of variations in case-mix and baseline risk), few common predictors for comparison and absence of well-defined subgroups, no formal meta-analysis nor comparison of variability and bias between studies was planned, as these comparisons are recognised as being prone to bias.[25] Qualitative comparisons are described considering major differences between populations and study design. Prevalence of severe disease was used to group studies into low (<2.5%), moderate (2.5%–7.5%) and high (>7.5%) prevalence settings, as a proxy for the case-mix and level of care.

Quality assessment

Risk of bias and applicability of studies were assessed using the QUIPS tool for prognostic factor studies,[16] and PROBAST for studies developing, validating or updating prediction models.[17] Each study was independently assessed using QUIPS or PROBAST by two reviewers (AC and RT), as well as an independent senior reviewer (MC, AVDB or JV). All discrepancies were resolved by discussion. For prognostic factor studies (QUIPS), risk of bias was categorised as low, medium or high, while in clinical prediction model studies (PROBAST) risk was categorised as low, high or unclear. For all studies, applicability was assessed as being of high, low or unclear concern.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report. The co-primary authors (AC and RT) had full access to the data and final responsibility for the decision to submit for publication.

Patient and public involvement

Neither patients nor members of the public were directly involved in the conduct of this work.

RESULTS

The electronic search retrieved 5930 articles, and 19 additional articles were identified through snowballing and expert consultation (figure 1). Eighteen studies were included in the review: 16 studies evaluated 200 prognostic factors, from 75 SNOMED-CT categories,[12 26–38] and eight evaluated 33 clinical prediction model/outcome pairs, using 25 distinct models.[27 29 31 38–42]

In total 24 530 children were included, with overlap across eight studies.[26 31 32 34–37 40] The majority (11/18) included only hospitalised patients. Two studies recruited children from primary care,[29 33] and five recruited both children admitted and those sent home directly from hospital outpatient or emergency departments.[28 35–37 40] Seven studies included children aged 5 years and under,[27 30 32–34 39 42] with the remainder including patients up to 19 years of age. Definition of fever varied between studies, ranging from an axillary temperature (or equivalent) of ≥37.5°C to >38.1°C. Five

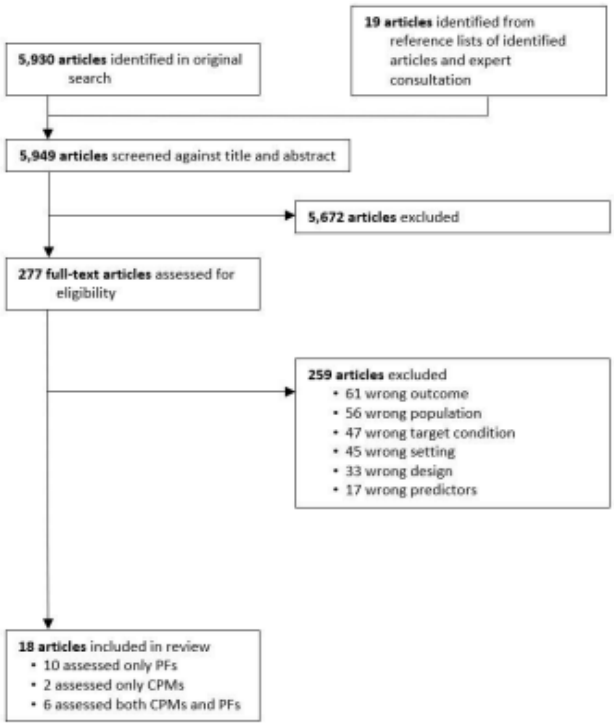

Figure 1 Selection of studies. Only one reason for exclusion per study is listed. CPM, clinical prediction model; PF, prognostic factor.

studies did not include a temperature measurement in their eligibility criteria and enrolled children on the basis of suspected infection or sepsis.[35 38 40–42] Eight studies were conducted in sub-Saharan Africa,[26 27 31–34 41 42] four in North America,[35–37 40] three in Europe,[29 30 38] two in Asia[12 39] and one in Latin America.[28] Six were multicentre studies.[12 26 31 33 40 42] Most used 'hard' outcomes to define severe disease, such as mortality, organ dysfunction or need for organ support, while four used 'softer' outcomes, such as prolonged length of stay or persistence of symptoms.[29 30 35 38] Characteristics of the 18 studies are summarised in table 1.

Prognostic factors

Figures 2–4 present prognostic factors identified as having rule-in (PLR ≥5.0) or rule-out (NLR ≤0.2) value in at least one study. Prognostic factors that met neither of these pre-specified cut-offs are presented in online supplemental appendix S5. In settings with moderate prevalence of severe disease, both high lactate (PLR range 4.97–5.13) and hypoglycaemia (PLR range 12.63–13.36) were useful for ruling in severe disease,[32 34 37] whereas a lactate ≤5 mM was more useful as a rule-out test (NLR 0.13) among a population in whom prevalence of severe disease was high (febrile children with signs of poor organ perfusion).[26]

Hypoxia was most useful to rule-in severe disease in moderate prevalence settings (PLR range 8.11–9.49).[27 34] Some studies found hypotension and bedside markers of poor peripheral perfusion to have useful rule-in value, but this was inconsistent (PLR range 1.89–9.57 and 1.78–17.38, respectively).[26 27 31 32 34–36 38] Bradycardia was evaluated in a multicentre study conducted across three East African countries and found to have useful rule-in value (PLR range 5.95–14.59) for severe disease in those high prevalence settings.[26 31] Impaired consciousness, assessed using bedside coma scales, was a useful predictor of severe disease, particularly in low and moderate prevalence settings (PLR range 3.38–14.02), with the post-test probability of poor outcome increasing with the degree of neurological impairment.[27 32 34 36 38 41 42]

In sub-Saharan African settings, severe malnutrition (PLR range 1.56–11.23),[26 27 32 34 41] HIV positive status (PLR range 2.32–12.48)[26 27 41 42] and bedside correlates of metabolic derangement such as deep breathing and jaundice (PLR range 3.57–7.71) were useful rule-in predictors, across a range of prevalence settings.[27 32 34]

Very few prognostic factors were satisfactorily able to rule-out progression to severe disease: presence of comorbidities (NLR range 0.12–1.04), sepsis at admission (NLR 0.19) and prostration (NLR range 0.18–1.23) were each identified in only one study.[27 28 35]

Clinical prediction models

Figure 5 illustrates the discrimination (AUROC) of 25 clinical prediction models for 33 different outcomes assessed in eight studies: most (18/33) were external validations of existing models[27 31 38 39]; 13 were newly derived models[29 31 40–42] and two were updates and external validations of an existing model.[38] Components of the clinical prediction models are summarised in table 2.

Three models, Lambaréné Organ Dysfunction Score (LODS), Paediatric Early Death Index for Africa (early death score) (PEDIA-e) and Signs of Inflammation in Children that Kill (SICK), showed good (AUROC ≥0.80) discrimination in a Ugandan setting where in-hospital mortality occurred at a prevalence of 4.7% (AUROC range 0.85–0.90).[27] Two of these (LODS and PEDIA-e) were also assessed in a multicentre study in East Africa where discrimination was lower (AUROCs of 0.77 and 0.70).[31] This study also derived two models, the FEAST-Paediatric Emergency Triage (FEAST-PET) and FEAST-Paediatric Emergency Triage and Laboratory (FEAST-PETaL) scores, which showed good discrimination (AUROCs of 0.86 and 0.82).[31] Two other East African studies used combinations of simple clinico-demographic variables to derive a number of prediction models, four of which had AUROCs ≥0.80.[41 42]

One North American study derived a model to predict hypotensive shock in unselected children presenting with suspected sepsis, which showed good discrimination in an external geographic validation (AUROC 0.87).[40] The Yale Observation Score also showed high discrimination for mortality (AUROC 0.97) and mechanical ventilation (AUROC 0.89) in India, however, the small sample size (n=100) renders the results difficult to interpret.[39] In general, models assessed against 'softer' outcomes (eg,

Table 1 Characteristics of included studies

Study (year); setting, country	Cohort	Design	Quality assessment		CPM or PF study*	Sample size	Population		Outcome	Outcome prevalence (n/N)
			Risk of bias	Applicability concern			Inclusion criteria	Exclusion criteria		
Outcomes including death, organ dysfunction, organ support and PICU admission										
Scott (2020)[40]; Secondary and tertiary care hospitals, USA	Hospital OPD/ED	Retrospective cohort	High	Low	CPM	2464	Age 60 days to 18 years; Clinician-suspected sepsis	Hypotensive septic shock on arrival;† transfer to another centre; leaving ED before formal evaluation; incorrect registration	Hypotensive septic shock‡≤24 hour	11.4% (282/2464)
Walia (2016)[39]; Tertiary care hospital, India	Hospitalised§	Prospective cohort	High	High	CPM	100	Age 3–36 months; Axillary temperature >36.9°C (early morning) or >37.4°C	Non-infectious cause of fever; immunisation ≤2 days; immunodeficiency, autoimmune disorder	In-hospital mortality; Mechanical ventilation	11.0% (11/100); 17.0% (17/100)
Aramburo (2018)[26]; Secondary and tertiary care hospitals, Kenya, Tanzania and Uganda	Hospitalised§	Randomised controlled trial	Moderate	High	PF	3008	Age 60 days to 12 years; history of fever or axillary temperature ≥37.5°C or <36°C; severe febrile illness¶	Non-infectious cause of illness; SAM, gastroenteritis, burns, chronic kidney disease, pulmonary oedema, intoxication, surgical conditions, receipt of isotonic fluids during the same illness	In-hospital mortality (72 hours)	10.3% (309/3008)
George (2015)[31]; Secondary and tertiary care hospitals, Kenya, Tanzania and Uganda	Hospitalised§	Randomised controlled trial	High	High	CPM	3121	Age 60 days to 12 years; history of fever or axillary temperature ≥37.5°C or <36°C; severe febrile illness¶	Non-infectious cause of illness; SAM, gastroenteritis, burns, chronic kidney disease, pulmonary oedema, intoxication, surgical conditions, receipt of isotonic fluids during the same illness	In-hospital mortality (48 hours)	9.8% (306/3121)
Scott (2012)[37]; Tertiary care hospital, USA	Hospital OPD/ED	Prospective cohort	High	High	PF	239	Age <19 years; temperature >38.5°C or <36°C and heart rate >2 SD above normal for age; underwent phlebotomy as part of usual care	Transfer from another health facility; known inborn errors of metabolism; receipt of >15 min of intravenous therapy	24 hours organ dysfunction	5.4% (13/239)

Continued

Table 1 Continued

Study (year); setting, country	Cohort	Design	Quality assessment		CPM or PF study*	Sample size	Population		Outcome	Outcome prevalence (n/N)
			Risk of bias	Applicability concern			Inclusion criteria	Exclusion criteria		
Scott (2014)[36]; Tertiary care hospital, USA	Hospital OPD/ED	Prospective cohort	High	High	PF	239	Age <19 years; temperature >38.5°C or <36°C and heart rate >2 SD above normal for age; undergoing phlebotomy as part of routine care	Transfer from another health facility; known inborn errors of metabolism; receipt of >15 min of intravenous therapy	24 hours organ dysfunction	5.4% (13/239)
Nadjm (2013)[34]; Secondary care hospital, Tanzania	Hospitalised§	Prospective cohort	Moderate	High	PF	3319	Age 2 months to 5 years; history of fever in last 48 hours or axillary temperature ≥37.5°C	Chronic illness (excluding HIV and malnutrition); trauma; surgical conditions	In-hospital mortality	5.1% (170/3319)
Mtove (2011)[32]; Secondary care hospital, Tanzania	Hospitalised§	Prospective cohort	Moderate	High	PF	3248	Age 2 months to 13 years; history of fever in last 48 hours or axillary temperature ≥37.5°C	Chronic illness (excluding HIV and malnutrition); trauma; surgical conditions	In-hospital mortality	5.0% (164/3248)
Lowlaavar (2016)[42]; Secondary and tertiary care hospitals, Uganda	Hospitalised§	Prospective cohort	High	High	CPM	1307	Age 6–60 months; admitted during study working hours or within 8 hours of study shift with a proven or suspected infection	Previous enrolment; residence outside study catchment area	In-hospital mortality	5.0% (65/1307)
Conroy (2015)[27]; Tertiary care hospital, Uganda	Hospitalised§	Prospective cohort	High	High	CPM	2502	Age 2 months to 5 years; history of fever in last 48 hours or axillary temperature >37.5°C	None reported	In-hospital mortality	4.7% (99/2089)
van Nassau (2018)[38]; Secondary care hospital, The Netherlands	Hospitalised§	Retrospective cohort	High	High	CPM	864	Age <18 years; suspected bacterial infection**	Surgical conditions	PICU transfer and/or in-hospital mortality	2.7% (24/864)

Continued

Table 1 Continued

Study (year); setting, country	Cohort	Design	Quality assessment		CPM or PF study*	Sample size	Population		Outcome	Outcome prevalence (n/N)
			Risk of bias	Applicability concern			Inclusion criteria	Exclusion criteria		
Scott (2017)[35]; Tertiary care hospital, USA	Hospital OPD/ED	Retrospective cohort	Low	High	PF	1299	Age 60 days to 18 years; suspected sepsis††; measurement of venous lactate as part of routine care within 8 hours of ED arrival	Transfer from another health facility	30-day mortality	1.9% (25/1299)
SEAIDCRN (2017)[12]; Tertiary care hospitals, Indonesia, Thailand and Vietnam	Hospitalised§	Prospective cohort	High	High	PF	763	Age 30 days to 18 years; modified SIRS criteria‡‡	Suspicion of hospital-acquired infection; admission to hospital within previous 30 days; transfer from another health facility after >72 hours admission; weight <3 kg; enrolment in another clinical study	28-day mortality	1.9% (14/731)
Costa de Santana (2017)[28]; Tertiary care hospital, Brazil	Hospital OPD/ED	Retrospective cohort	High	High	PF	254	Age <13 years; axillary temperature >38.5°C; measurement of respiratory rate and heart rate on three occasions in absence of fever; measurement of leucocyte count as part of routine care	Congenital malformations; bronchopulmonary dysplasia; medullary aplasia; cardiac, renal or hepatic insufficiency	In-hospital mortality	1.6% (4/254)
Kwizera (2019)[41]; Secondary care hospital, Rwanda	Hospitalised§	Prospective cohort	High	High	CPM	949	Age 28 days to 18 years; confirmed acute infectious disease; symptom onset <14 days prior to hospital admission	Allergy to antimicrobials to treat sepsis (antibiotics, artesunate, artemether-lumefantrine); terminal disease	In-hospital mortality	1.5% (14/949)
Outcomes including length of stay and persistence of symptoms										
Freyne (2013)[30]; Secondary care hospital, Ireland	Hospitalised§	Prospective cohort	High	High	PF	46	Age 6–36 months; axillary temperature >38.1°C	Chronic illness; immunisation ≤2 days, antipyretic use ≤2 hours	Length of stay >96 hours	26.1% (12/46)

Continued

Table 1 Continued

Study (year); setting, country	Cohort	Design	Quality assessment		CPM or PF study*	Sample size	Population		Outcome	Outcome prevalence (n/N)
			Risk of bias	Applicability concern			Inclusion criteria	Exclusion criteria		
van Nassau (2018)[38]; Secondary care hospital, The Netherlands	Hospitalised§	Retrospective cohort	High	High	CPM	864	Age <18 years; suspected bacterial infection**	Surgical conditions	Length of stay ≥7 days	22.2% (179/806)
Elshout (2015)[29]; General Practice (out of hours), The Netherlands	Primary care	Prospective cohort	High	High	PF	480	Age 3 months to 6 years; history of fever	Communication in Dutch not possible; enrolment in last 2 weeks; direct referral to hospital required	Persistent fever at D3	13.1% (63/480)
Mwandama (2016)[33]; Community Health Workers, Malawi	Primary care	Prospective cohort	High	High	PF	285	Age 2–59 months; history of fever in last 48 hours or temperature ≥37.5°C; negative malaria rapid diagnostic test	Receipt of antimalarial in last 2 weeks; presence of danger signs§§	Persistent symptoms at D7	10.4% (19/182)

Studies are grouped according to the type of outcome they used: 'hard' (death, organ dysfunction, organ support, PICU admission) or 'soft' (length of stay, persistence of symptoms).
*Studies evaluating both PFs and CPMs were categorised on the basis of their primary analysis to facilitate review using the appropriate quality assessment tool.
†Hypotensive systolic blood pressure on arrival with receipt of a fluid bolus or vasoactive agent within 30 min.
‡Hypotension plus receipt of ≥30 mL/kg isotonic crystalloids or vasoactive medication.
§Only children the treating physician decided to admit were eligible but recruitment occurred at the time of admission to the health facility.
¶Respiratory distress (increased work of breathing or deep breathing) and/or impaired consciousness (coma or prostration) AND evidence of poor peripheral perfusion (capillary refill time >2 s or lower limb temperature gradient or weak radial pulse or severe tachycardia).
**Initiation of antibiotics within 24 hours of arrival in the emergency department.
††Decreased mental status or perfusion in the setting of suspected infection.
‡‡Rectal temperature >38.5°C or <35°C (or equivalent) AND heart rate >2 SD above normal for age (unless hypothermic) AND respiratory rate >2 SD above normal for age AND altered mental status OR systolic blood pressure <2 SD below normal for age OR pulse pressure <20 mm Hg OR capillary refill time >2 s OR SpO_2 <95% OR leucocyte count >12×10^3 cells/µL or <5×10^3 cells/µL.
§§Convulsions, repeated vomiting, lethargy, severe anaemia or loss of consciousness.
CPM, clinical prediction model; ED, emergency department; n, number of outcomes; n, number of cases; OPD, outpatient department; PF, prognostic factor; PICU, paediatric intensive care unit; SAM, severe acute malnutrition; SEAIDCRN, Southeast Asia Infectious Disease Clinical Research Network; SIRS, systemic inflammatory response syndrome.;

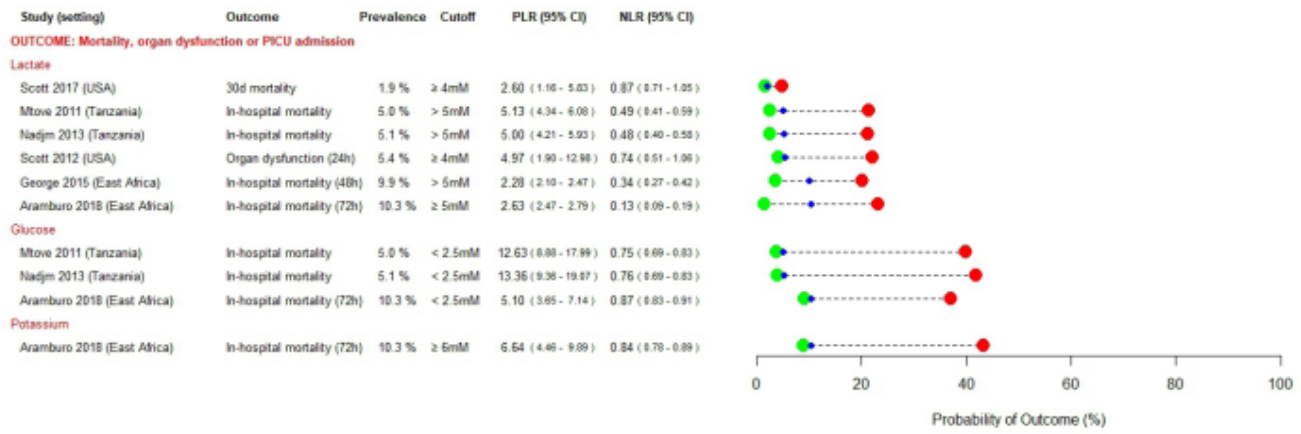

Figure 2 Prognostic factors identified as having rule-in (PLR ≥5.0) or rule-out (NLR ≤0.2) value for severe disease in at least one study—laboratory tests. mM, millimolar; NLR, negative likelihood ratio; PICU, paediatric intensive care unit; PLR, positive likelihood ratio.

persistence of symptoms or length of stay) had poorer discrimination, and a more distal temporal relationship between measurement of predictors and ascertainment of outcome.

Quality assessment

Only one prognostic factor study was at low risk of bias,[35] while another was judged to be at low risk of bias in all but one domain.[26] The domains at highest risk of bias were study confounding, related to omission of important covariates; study participants, often due to requirement for the measurement of specific laboratory parameters (eg, leucocyte count); and statistical analysis, as a result of inadequate reporting or inappropriate exclusion of participants from the analysis (figure 6).

Each clinical prediction model/outcome pair was assessed independently and all judged to be at high risk

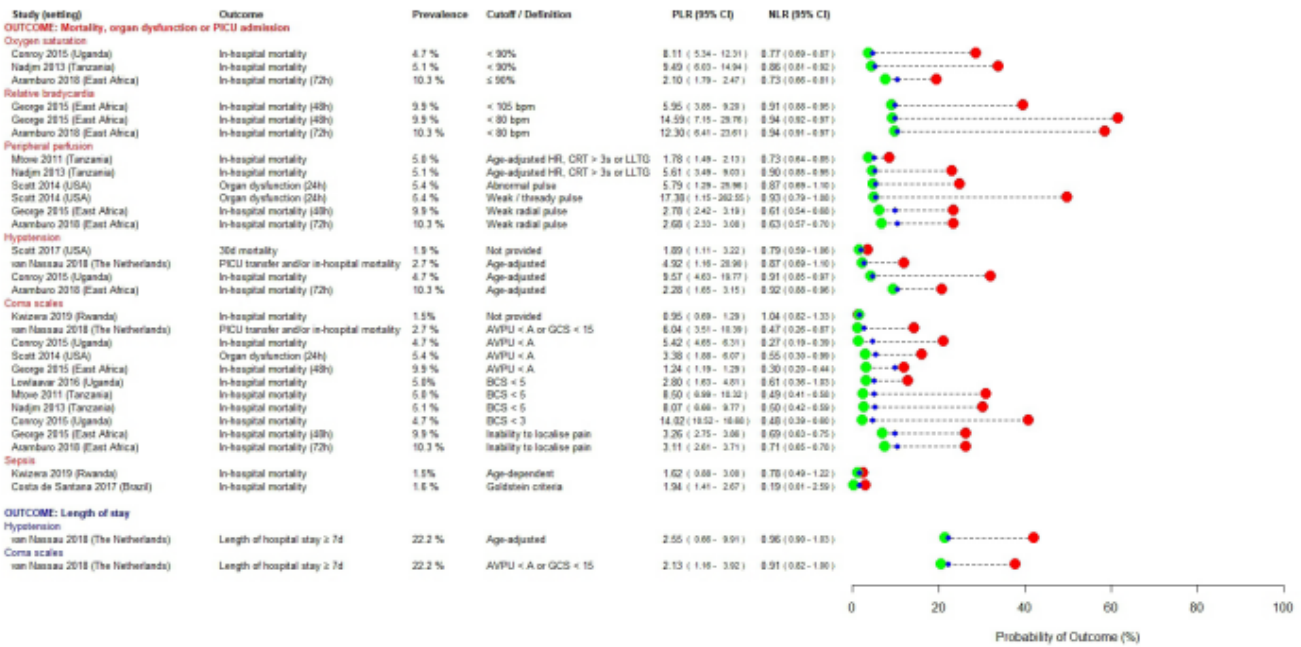

Figure 3 Prognostic factors identified as having rule-in (PLR ≥5.0) or rule-out (NLR ≤0.2) value for severe disease in at least one study—cardiovascular, respiratory or neurological signs. in the study by Costa *et al*. 'sepsis' was defined according to the systemic inflammatory response syndrome (SIRS), requiring measurement of heart rate, respiratory rate, temperature and leucocyte count. In the study by Kwizera *et al*, 'sepsis' was defined according to the qSOFA Score in children aged ≥15 years, and using a combination of temperature, mental status, respiratory distress, prostration and seizures in children aged <15 years. AVPU, alert, voice, pain or unresponsive; BCS, Blantyre Coma Score; bpm, beats per minute; CRT, capillary refill time; GCS, Glasgow Coma Score; HR, heart rate; LLTG, lower limb temperature gradient; NLR, negative likelihood ratio; PICU, paediatric intensive care unit; PLR, positive likelihood ratio; qSOFA, quick Sequential Organ Failure Assessment.

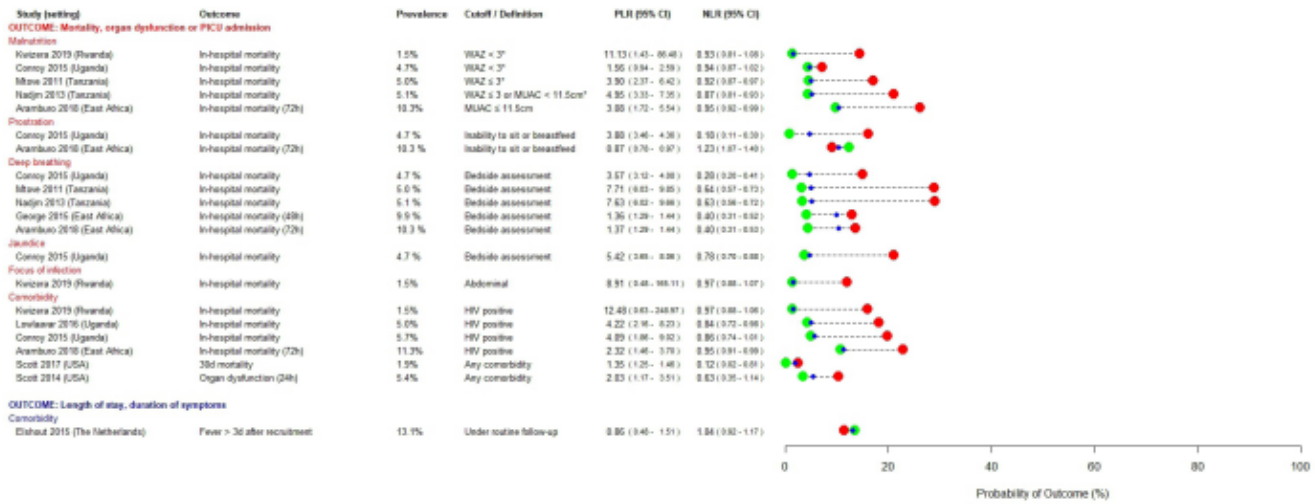

Figure 4 Prognostic factors identified as having rule-in (PLR ≥5.0) or rule-out (NLR ≤0.2) value for severe disease in at least one study—historical, anthropometric and metabolic variables. *Children with visible wasting or nutritional oedema were also classified as having severe malnutrition. In the study by Elshout *et al*, 'comorbidity' was defined as being under routine care of a paediatrician or ENT specialist. ENT, ear, nose and throat; MUAC, mid-upper arm circumference; NLR, negative likelihood ratio; PICU, paediatric intensive care unit; PLR, positive likelihood ratio; WAZ, weight-for-age z-score.

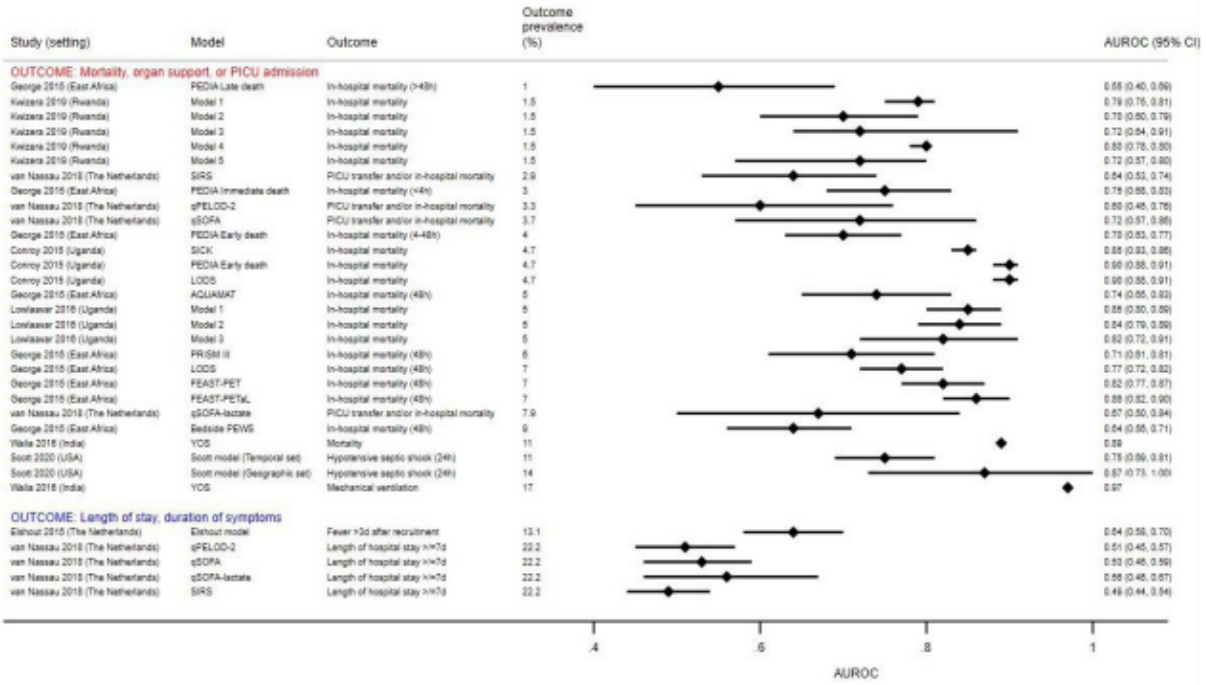

Figure 5 Discrimination of clinical prediction models to identify children at risk of severe disease. Individual studies evaluated different clinical prediction models using datasets with varying numbers of children with severe disease, depending on the data available. The outcome prevalence reflects the proportion of children with severe disease in the dataset used to evaluate that particular prediction model/outcome pair. This may be different from the overall prevalence of children with severe disease in the study, which is listed in table 1 and used to classify studies into low, moderate or high prevalence settings. No CIs were provided for the AUROC estimates in the study by Walia *et al*. AQUAMAT, African Quinine Artesunate Malaria Trial; AUROC, area under the receiver operating characteristic curve; FEAST-PET, FEAST-Paediatric Emergency Triage; FEAST-PETaL, FEAST-Paediatric Emergency Triage and Laboratory; LODS, Lambaréné Organ Dysfunction Score; PEDIA, Paediatric Early Death Index for Africa; PEWS, Paediatric Early Warning Score; PICU, paediatric intensive care unit; PRISM III, Paediatric Risk of Mortality; qPELOD-2, quick Paediatric Logistic Organ Dysfunction; qSOFA, quick Sequential Organ Failure Assessment; SICK, Signs of Inflammation in Children that Kill; SIRS, Systemic Inflammatory Response Syndrome; YOS, Yale Observation Score.

Table 2 Components of clinical prediction models evaluated in the included studies

Clinical prediction model	Variables used in the clinical prediction model in the included studies	Included study evaluating the model	Original study developing the model
AQUAMAT	Base deficit, impaired consciousness, convulsions, elevated blood urea, underlying chronic illness	George[31]	von Seidlein[60]
ELSHOUT model	Sore throat, palpable lymph nodes, duration of fever before consultation, C-reactive protein	Elshout[29]	Elshout[29]
FEAST-PET	Axillary temperature, heart rate, capillary refill time, conscious level, respiratory distress, lung crepitations, severe pallor, weak pulse	George[31]	George[31]
FEAST-PETaL	FEAST-PET with the addition of lactate, pH, blood urea nitrogen	George[31]	George[31]
KWIZERA model 1	Age, respiratory rate, heart rate, temperature, capillary refill time, altered mental state	Kwizera[41]	Kwizera[41]
KWIZERA model 2	Age, respiratory rate, heart rate, capillary refill time, altered mental state	Kwizera[41]	Kwizera[41]
KWIZERA model 3	Age, respiratory rate, temperature, capillary refill time, altered mental state	Kwizera[41]	Kwizera[41]
KWIZERA model 4	Age, respiratory rate, capillary refill time, altered mental state	Kwizera[41]	Kwizera[41]
KWIZERA model 5	Age, respiratory rate, altered mental state	Kwizera[41]	Kwizera[41]
LODS	Deep breathing, coma, and prostration	George[31]; Conroy[27]	Helbok[50]
LOWLAAVAR model 1	Conscious level, HIV, weight-for-age z-score	Lowlaavar[42]	Lowlaavar[42]
LOWLAAVAR model 2	Conscious level, HIV, mid-upper arm circumference	Lowlaavar[42]	Lowlaavar[42]
LOWLAAVAR model 3	Conscious level, mid-upper arm circumference	Lowlaavar[42]	Lowlaavar[42]
PEDIA-i	Anaemia, jaundice, indrawing, deep breathing, conscious level, prostration, convulsions/seizures, temperature	George[31]	Berkley[51]
PEDIA-e	Jaundice, indrawing, conscious level, prostration, convulsions/seizures, wasting, kwashiorkor*	George;[31] Conroy[27]	Berkley[51]
PEDIA-l	History >7 days, conscious level, prostration, convulsions/seizures, temperature, wasting, kwashiorkor	George[31]	Berkley[51]
PEWS†	Heart rate, capillary refill time, respiratory rate, oxygen saturation, systolic blood pressure	George[31]	Parshuram[61]
PRISM III‡	Heart rate, temperature, conscious level, systolic blood pressure, glucose, potassium, PCO_2, pH, acidosis, pupillary reflexes	George[31]	Pollack[62]
qPELOD-2	Systolic or mean arterial pressure, heart rate, altered mentation	van Nassau[38]	Leclerc[53]
qSOFA	Respiratory rate, altered mentation, systolic blood pressure	van Nassau[38]	Seymour[54]
qSOFA-L	qSOFA with the addition of lactate	van Nassau[38]	van Nassau[38]

Continued

Table 2 Continued

Clinical prediction model	Variables used in the clinical prediction model in the included studies	Included study evaluating the model	Original study developing the model
SCOTT model	Systolic blood pressure, diastolic blood pressure, temperature, age, respiratory rate, heart rate, arrival via emergency medical services, oncological comorbidity, indwelling central line on arrival, hospitalised in the last year	Scott[40]	Scott[40]
SICK	Level of consciousness, temperature, heart rate, respiratory rate, systolic blood pressure, SpO_2, capillary refill time, age	Conroy[27]	Kumar[52]
SIRS	Heart rate, respiratory rate, leucocyte count, temperature	van Nassau[38]	Goldstein[63]
YOS	Quality of cry, reaction to parent stimulation, state variation, colour, hydration, response to social overtures	Walia[39]	McCarthy[64]

*Kwashiorkor was not included in the PEDIA-e score in the Conroy *et al* study.
†Receipt of oxygen therapy and respiratory effort included in the original PEWS but not measured in the George *et al* study.
‡Pupillary reflexes, pH, total CO_2, arterial PaO_2, creatinine, urea, white blood cells, prothrombin time and platelets included in the original PRISM III score but not measured in the George *et al* study.
AQUAMAT, African Quinine Artesunate Malaria Trial; FEAST-PET, FEAST-Paediatric Emergency Triage; FEAST-PETaL, FEAST-Paediatric Emergency Triage and Laboratory; LODS, Lambaréné Organ Dysfunction Score; PEDIA-e, Paediatric Early Death Index for Africa (early death score); PEDIA-i, Paediatric Early Death Index for Africa (immediate death score); PEDIA-l, Paediatric Early Death Index for Africa (late death score); PEWS, Paediatric Early Warning Score; PRISM-III, Paediatric Risk of Mortality; qPELOD-2, quick Paediatric Logistic Organ Dysfunction; qSOFA, quick Sequential Organ Failure Assessment; qSOFA-L, quick Sequential Organ Failure Assessment-Lacate; SICK, Signs of Inflammation in Children that Kill; SIRS, Systemic Inflammatory Response Syndrome; YOS, Yale Observation Score.

of bias (figure 6). Most often this was due to inadequate reporting of model performance (studies reporting discrimination but not calibration), circularity between predictors and outcomes or having fewer than 100 participants with severe outcomes for model validation. It is noteworthy that one study which externally validated three models included 99 children who died.[27] Another study which derived and/or validated nine models undertook an additional external validation in a population of acutely unwell but non-febrile children (and thus not eligible for consideration in this review), which included more than 100 children who died.[31]

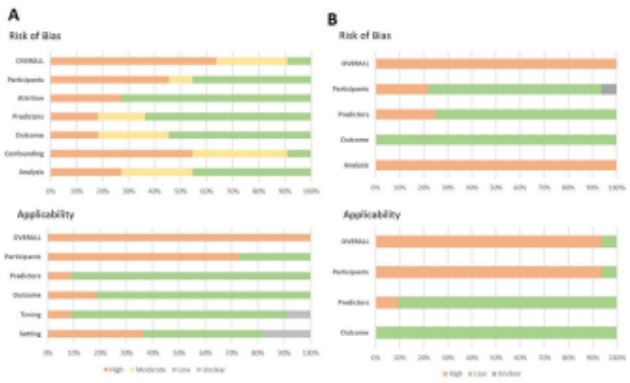

Figure 6 Risk of bias and applicability assessments for included studies using (A) the QUIPS tool (n=11 studies) and (B) PROBAST (n=33 clinical prediction model/outcome pairs from seven studies). All studies evaluating clinical prediction models were assessed using PROBAST, except for the study by Elshout *et al*, which was primarily a prognostic factor study and was therefore assessed using QUIPS. PROBAST, Prediction Model Risk of Bias Assessment Tool; QUIPS, Quality In Prognosis Studies.

In all but one study there was high concern regarding applicability to the review question.[40] This was largely due to the majority of studies including only children requiring hospitalisation, with recruitment occurring after the decision to admit had been made by the treating physician. Full details on risk of bias and applicability assessments are provided in online supplemental appendix S6.

DISCUSSION

This systematic review of prognostic factors and clinical prediction models assessing severity of disease in febrile children highlights that few well-conducted studies address this important public health question, particularly in unselected children presenting from the community. One of its main strengths is the inclusion of studies from a wide geographic context, aiding understanding of how predictive performance can vary across settings. By focusing on prognosis, we identified features that predict the likelihood that a child's illness might progress, rather than features associated with illness severity at the moment of assessment.

Most prognostic factors identified as valuable for predicting severe childhood febrile illness (PLR ≥5.0) overlapped with individual components of the most

promising clinical prediction models (AUROC ≥0.80): nutritional and HIV status, hypoxia, altered consciousness, and markers of acidosis (raised venous lactate or deep breathing) and poor peripheral perfusion (weak pulse, limb-core temperature gradient or prolonged capillary refill time).[27 31 32 34 36 38 42] Hypoglycaemia was a useful prognostic factor identified in our review, but omitted in most clinical prediction models. Many of these features, however, indicate a child that is already very unwell, reflecting the fact that most studies included only hospitalised children and focused on predicting mortality. Few prognostic factors adequately ruled-out (NLR ≤0.2) the possibility of progression to severe disease, a finding consistent with a previous systematic review evaluating the diagnostic utility of clinical features for serious bacterial infections.[10]

The major limitation of our work arises from the heterogeneity of studies, which precludes comparison of effect estimates. Second, it is difficult to determine if studies included children presenting to first-line health workers. We did not exclude studies solely based on the designated 'level' of a health facility: concerned parents in all settings use primary, secondary and tertiary care facilities as their first point-of-access. Third, most studies included only hospitalised children. This is a major barrier to understanding the potential for prognostic factors and prediction models to guide referral or admission decisions. Follow-up of children assessed as 'low-risk' (ie, those managed in the community) must be a priority for future studies seeking to determine the validity of prognostic factors and prediction models in outpatient settings.[43] Fourth, in line with other reviews we found most studies to be of low quality.[44] Recent guidance may help address this.[17] Finally, we framed the review around 'febrile illness', rather than, for example, 'clinically-suspected infection'. Our rationale was to ensure the findings were as relevant as possible for lesser-trained community health workers in resource-constrained settings, for whom a presumptive diagnosis of suspected infection can be challenging. Febrile illness is an accepted 'pragmatic point-of-entry' in these settings,[45] however, we acknowledge that some children (particularly younger infants) may not mount a fever in response to serious infection. Therefore, despite our deliberately broad definition of febrile illness (documented abnormal temperature and history of fever), and the inclusion of studies of children with 'suspected sepsis', relevant studies may have been missed. Of note, in view of a suggestion arising during the peer-review process we also performed a second MEDLINE search, using alternate search strings, which did not yield any additional eligible articles (online supplemental appendix S7).

Thirty out of 200 (15%) prognostic factors met our prespecified threshold for clinical relevance (PLR ≥5.0 or NLR ≤0.2). This may reflect the difficulty of identifying parsimonious predictors for all febrile children. While common pathophysiological pathways for severe disease have been identified across a spectrum of microbial aetiologies,[46 47] certain predictors may perform better for specific syndromes or pathogens, compared with all-cause febrile illness. Five studies in our review reported a high proportion of children as being either slide-positive or rapid diagnostic test-positive for malaria. Notwithstanding the issues of co-infection and/or concomitant incidental parasitaemia in settings of high malaria endemicity, it is possible that the findings of these studies are more pertinent to children with malaria. However, four of these studies compared the prognostic performances of hyperlactaemia, hypoglycaemia and the prediction models SICK, LODS and PEDIA, and found them to be broadly consistent between children with malaria, non-malarial fever and invasive bacterial disease.[26 27 32 34] Furthermore, as can be seen in figures 2–4, a number of predictors identified in malaria endemic regions also demonstrated prognostic utility in contexts where malaria is not endemic (eg, venous lactate, impaired peripheral perfusion, hypotension and altered consciousness). This, in conjunction with the subgroup analyses performed in the original studies, gives us a degree of confidence that the prognostic factors that we have identified are generalisable across different infecting pathogens. Nonetheless, future reviews using search strategies developed to retrieve syndrome-specific or pathogen-specific studies should explore this.

Another potential explanation for the relatively few valuable prognostic factors identified is work-up bias. In most studies, predictors were available to the treating clinicians: abnormal values are likely to have been acted on and predictive performance underestimated. For most predictors, particularly clinical signs, this is unavoidable as blinding is often neither possible nor ethical. When feasible, randomisation is required to definitively assess their potential impact.[48] This is particularly important for new tests proposed in resource-limited settings. For example, both lactate and hypoxia were identified as potentially of value in this review but introducing tests for these parameters at all first-line health facilities across the tropics would incur substantial cost, and as their predictive value may vary in different settings, could result in unnecessary or missed referrals. Randomisation can help determine whether new tests such as these add value to simple clinical assessment.[49]

Clinical prediction models performed better when derived and validated in similar populations[27]: in East Africa LODS and PEDIA-e (both derived in sub-Saharan Africa)[50 51] were superior to SICK (originally derived in India).[52] Model performance also improved when predicting the same outcome as the derivation study: quick Sequential Organ Failure Assessment and quick Paediatric Logistic Organ Dysfunction, derived to predict mortality, performed poorly when predicting prolonged length of stay.[38 53 54] These findings highlight the importance of deriving prediction models using populations and outcomes appropriate to the clinical question. While mortality is a 'hard' outcome, it seldom occurs in primary care. Furthermore, its reflection of disease

severity is influenced (mediated) by the level of care. It is striking that in Tanzania a raised lactate conveyed a post-test probability of in-hospital mortality comparable to that of 'organ dysfunction within 24 hours of arrival' in a similar prevalence setting in the USA.[32 34 37] Rather than relying on models derived in secondary care to generalise to outpatient settings across different epidemiological landscapes, alternative ways to quantify disease severity, which consider local context yet avoid circularity between predictor variables and outcome definitions, will be important to facilitate comparisons across settings and explore generalisability of risk prediction tools. Finally, the fact that most studies summarised model performance using only the AUROC means that is difficult to appreciate what the impact might be on clinical decision making.[55]

In LMIC primary care contexts, many variables are not feasible to collect,[56] and as noted above, some may incur substantial cost. Interestingly, HIV and nutritional status were both identified in our review and represent the only prognostic factors meeting our threshold for clinical relevance that may not necessarily reflect a child that is overtly very unwell. While biological plausibility for the prognostic utility of these two variables is high, it should be noted that the study which identified them was small and correspondingly the CI for the PLR is wide.[41] The WHO's Integrated Management of Childhood Illnesses 'Danger Signs' are recommended to guide referrals from community healthcare providers in resource-constrained settings.[57] Of these, only altered consciousness was widely represented among included studies, and most found it to be a good predictor of severe disease.[26 27 31 32 34 36 38 41 42] History of convulsions was examined in two studies while other 'Danger Signs' were not evaluated.[26 27]

CONCLUSION

Our findings emphasise the limitations of individual prognostic factors. Performance varies widely across settings and clinicians must be cognisant not to over interpret individual predictors. While prediction models can support clinical decision making, they must be derived and validated using appropriate methodology, and populations and outcomes relevant to the clinical problem. For the identification of children at risk of severe febrile illness, this will require multiple, large, collaborative, research initiatives across different settings, which collect harmonised data on predictors and outcomes,[58 59] and include unselected children presenting from the community.

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Contributors AC conceived the study; AC, RT, YL, PT and KK defined the review strategy; AC and RT conducted the search, screened retrieved articles and extracted the data; AC, RT, MC, AVDB and JV assessed quality of included articles; AC and RT analysed the data and drafted the report; CK provided statistical oversight; PT and KK commented on the drafted report; AC, RT, MC, AVDB, JV, CK, NS, YL, PT and KK commented on and approved the final manuscript.

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5.2. Development of ePOCT+ and the medAL-suite

Title	ePOCT+ and the medAL-*suite*: Development of an electronic clinical decision support algorithm and digital platform for pediatric outpatients in low- and middle-income countries
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RT contribution	Conceptualization, formal analysis, investigation, methodology, software development, visualization, writing original draft, review and editing

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RESEARCH ARTICLE

ePOCT+ and the medAL-*suite*: Development of an electronic clinical decision support algorithm and digital platform for pediatric outpatients in low- and middle-income countries

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Abstract

Electronic clinical decision support algorithms (CDSAs) have been developed to address high childhood mortality and inappropriate antibiotic prescription by helping clinicians adhere to guidelines. Previously identified challenges of CDSAs include their limited scope, usability, and outdated clinical content. To address these challenges we developed ePOCT+, a CDSA for the care of pediatric outpatients in low- and middle-income settings, and the medical algorithm suite (medAL-*suite*), a software for the creation and execution of CDSAs. Following the principles of digital development, we aim to describe the process and lessons learnt from the development of ePOCT+ and the medAL-*suite*. In particular, this

material 3 is publicly available from Zenodo: DOI: 10.5281/zenodo.400380.

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work outlines the systematic integrative development process in the design and implementation of these tools required to meet the needs of clinicians to improve uptake and quality of care. We considered the feasibility, acceptability and reliability of clinical signs and symptoms, as well as the diagnostic and prognostic performance of predictors. To assure clinical validity, and appropriateness for the country of implementation the algorithm underwent numerous reviews by clinical experts and health authorities from the implementing countries. The digitalization process involved the creation of medAL-*creator*, a digital platform which allows clinicians without IT programming skills to easily create the algorithms, and medAL-*reader* the mobile health (mHealth) application used by clinicians during the consultation. Extensive feasibility tests were done with feedback from end-users of multiple countries to improve the clinical algorithm and medAL-*reader* software. We hope that the development framework used for developing ePOCT+ will help support the development of other CDSAs, and that the open-source medAL-*suite* will enable others to easily and independently implement them. Further clinical validation studies are underway in Tanzania, Rwanda, Kenya, Senegal, and India.

Author summary

In accordance with the principles of digital development we describe the process and lessons learnt from the development of ePOCT+, a clinical decision support algorithm (CDSA), and medAL-suite, a software, to program and implement CDSAs. The clinical algorithm was adapted from previous CDSAs in order to address challenges in regards to the limited scope of illnesses and patient population addressed, the ease of use, and limited performance of specific algorithms. Clinical algorithms were adapted and improved based on considerations of what symptoms and signs would be appropriate for primary care health workers, and how well these clinical elements predic a particular disease or severe outcome. We hope that by sharing our multi-stakeholder approach to the development of ePOCT+, it can help others in the development of other CDSAs. The medAL-*creator* software was developed to allow clinicians without IT programming experience to program the clinical algorithm using a drag-and-drop interface, intended to allow a wider range of health authorities and implementers to develop and adapt their own CDSA. The medAL-*reader* application, deploys the algorithm from medAL-*creator* to end-users following the usual healthcare processes within a consultation.

Introduction

Electronic clinical decision support algorithms (CDSAs) have been implemented in low- and middle-income countries (LMICs) in order to address excessive mortality due to poor quality of health care [1], and antimicrobial resistance due to inappropriate antibiotic prescription [2–5]. Such tools provide guidance through every step of the outpatient consultation to ultimately suggest the diagnosis and management plan based on the entered symptoms, signs and test results [6]. CDSAs have shown to help clinicians better adhere to guidelines [7–9], which resulting in improved quality of care and, for some, more rational antibiotic prescription [10,11]. This has led the World Health Organization (WHO) and its Member States to prioritize the scale-up of digital health technologies [12,13].

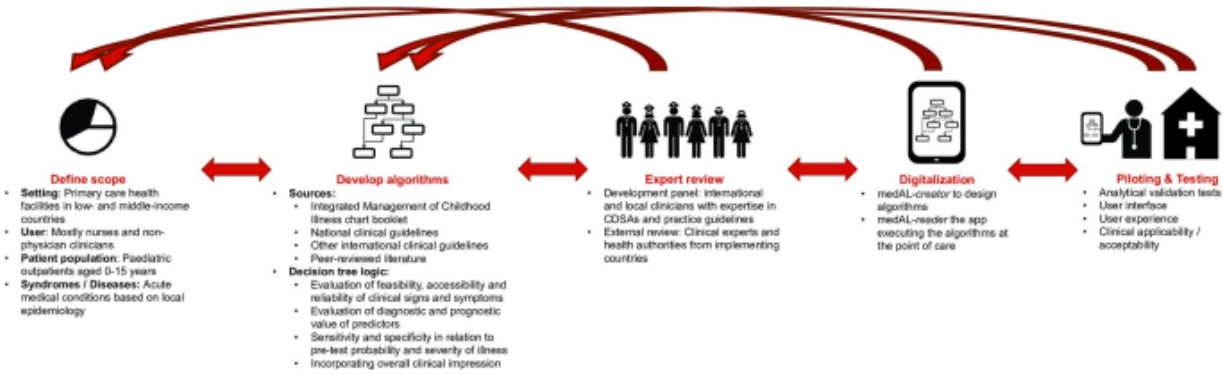

Fig 1. Overall development process of ePOCT+ requiring multiple feedback loops. The development process of ePOCT+ was an iterative process. We first defined the scope, then developed the algorithm (decision tree logic), followed by expert review with relevant stakeholders, the digitalization, and finally piloting and testing. Each stage resulted in multiple feedback loops to refine the end product.

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Current CDSAs are not standardized, and concerns have been raised about their limited demographic and clinical scope [14,15], their usability [15,16], and their static and generic logic based on outdated guidelines that are unable to adapt to new evidence, evolving epidemiology, or changing resources. These challenges may contribute to variable uptake of CDSAs [16–18], and suboptimal performance when implemented [9,19].

In order to address these challenges, and build on the experience of previous CDSAs by our group [10,11], and others [6,9], we developed the CDSA ePOCT+, and a supporting digital software to create and execute CDSAs, the medAL-*suite*. ePOCT+ is currently being implemented in over 200 health facilities within the context of implementation studies in Tanzania, Rwanda, Senegal, Kenya and India. Following the principles of digital development and guidance on CDSAs [20–22], we aim to transparently share the rationale, strategy, and lessons learnt from this development process (Fig 1).

Methods

Scope

Compared to our previous generation CDSAs [6,10,11], the target level of care (primary health care facilities), and target users (mostly nurses and non-physician clinicians) remain the same. However, the target patient population was expanded from 2 months to 5 years, to also cover young infants below 2 months, and in some countries children 5 years up to 15 years.

The expanded target population age group adds young infants (<2 months) who are at highest risk of mortality [23], and children aged 5–15 years who are often neglected in international and national policies resulting in a slower decrease in mortality in LMICs compared to children under 5 years [24]. This expanded age group may help address the challenge of uptake by avoiding the need for clinicians to change tools when managing children of different age groups.

The scope of illnesses covered was also expanded in response to the frustration of clinicians using CDSAs who were not able to reach specific illnesses [14,16]. Expanding the scope allowed for the integration of common illnesses covered by other national clinical guidelines to which clinicians are expected to adhere, and to provide more opportunity for antibiotic stewardship when providing management guidance for specific illnesses.

Three major criteria were considered when expanding the scope of illnesses: 1) Incidence of presenting symptoms and diagnoses; 2) Morbidity, mortality, and outbreak potential; and 3) Capacity to diagnose and manage specific conditions at the primary care level.

Additional conditions were identified through: 1) national guidelines; 2) fever aetiology studies; 3) national health surveys; 4) chief complaints from primary care outpatient studies; 5) clinical expert review teams from the implementation countries; 6) interviews with end user clinicians; and 6) observation of consultations at primary health care facilities (Table A in S1 Appendix). Examples of notable additions for the Tanzanian algorithm include trauma, urinary tract infection, and abdominal pain that can account for 4.3–21.6% [25], 5.9–19.7% [25–27], and 4.6–23% [11,26] of outpatient consultations respectively.

Clinical algorithm

The target users (mostly nurses and non-physician clinicians), and setting (primary health care facilities) were important considerations when identifying the guidelines and evidence to develop the algorithm. Previously validated algorithms [11], and the WHO Integrated Management of Childhood Illnesses (IMCI) chart booklets formed the backbone of the algorithm [28]. To support the expanded clinical scope, we turned to national guidelines to ensure adaptation to the local epidemiology, resources, and setting. If there was not sufficient detail in order to derive decision logic from these national guidelines, a brief review of literature was conducted to identify peer-reviewed literature and other international guidelines.

In order to transform narrative guidelines into Boolean decision tree logic algorithms, considerable interpretation was needed. The guiding principles for this process were derived from the properties to consider in the screening and diagnosis of a disease by Sackett and colleagues [29], the target product profile (TPP) for CDSAs as defined by experts in the field [21], and guidance on appropriate diagnostic and prognostic model development [30]. These include consideration of: a) the feasibility, acceptability, and reliability of clinical elements assessed at the primary care level, b) the diagnostic and prognostic value of individual and combined predictors, c) the sensitivity and specificity in relation to the severity and pre-test probability of the condition in the target population, and d) the overall clinical impression of the patient by the clinician.

a) Feasibility, acceptability, and reliability of predictors

If clinical algorithms are to be adequately utilized, the signs and symptoms used to reach a diagnosis must be feasible, acceptable and reliable when assessed by end-users. These properties were evaluated based on the results of several assessments: primarily an international Delphi study on predictors of sepsis in children [31], a systematic review on triage tools in low-resource settings [32], signs and symptoms included in established guidelines for primary health care workers such as IMCI [28], interviews with clinicians, observation of routine consultations, a Delphi survey among 30 Tanzanian health care workers (S2 Appendix), as well as subsequent feasibility tests observing clinicians using the CDSA on real and fictional cases. Notable findings from this process led to us not adding a pain score, capillary refill time, the assessment of cool peripheries, and weak and fast pulse, as they were deemed neither feasible nor reliable to be assessed at the primary care level. Importantly, these symptoms and signs are also not included within IMCI, likely for similar reasons [28].

b) Diagnostic and prognostic value of predictors

In the absence of validated diagnostic models for each diagnosis, we assessed individual diagnostic and prognostic factors to help guide the development of ePOCT+. Diagnostic studies derived from the population and setting of interest were preferred [33,34], as those developed from other settings often perform worse [35]. However, diagnostic predictors notably those predicting 'serious bacterial infection', often have low sensitivity, lack reference tests to

confirm bacterial origin, and ignore serious infections caused by viral diseases [36,37]. Prognostic studies are often better suited to develop clinical algorithms in order to understand which children are at risk of developing severe disease, regardless of the aetiology, to improve patient outcomes and reduce resource misallocation [38–40]. A systematic review of predictors of severe disease in febrile children presenting from the community helped identify useful clinical feature to be integrated within ePOCT+ [35], however few studies occurred at the primary care level. To address this gap we performed an exploratory analysis of clinical elements used in two CDSAs evaluated in Tanzania to predict clinical failure (S3 Appendix). This analysis found IMCI danger signs, severe general appearance, mid-upper arm circumference <12.5cm, oxygen saturation <90%, respiratory distress, and signs of anaemia and dehydration to be good predictors of clinical failure. Specific subgroup analyses on our previous generation CDSA provided further support for maintaining or modifying specific algorithm branches, particularly the inclusion of C-reactive Protein (CRP) point-of-care tests that helped safely reduce antibiotic prescription and improve confidence in management [41,42].

c) Sensitivity and specificity of algorithm branches in relation to severity and pre-test probability of condition

When constructing the algorithm, it was important to first identify children presenting with a severe condition, and only then use more specific branches to distinguish conditions requiring specific treatment from self-limiting illnesses requiring only supportive care (Fig 2). Predictors of severe conditions need to be sufficiently sensitive to guide interventions to

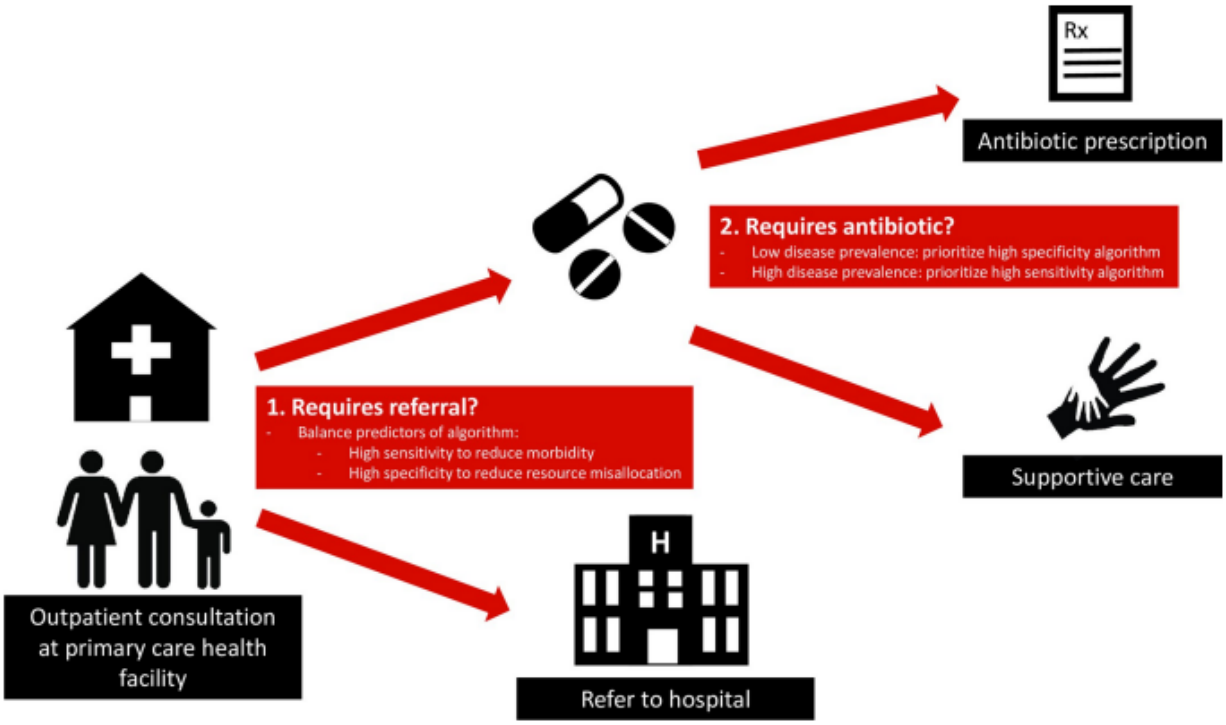

Fig 2. Considering algorithm performance in regards to pre-test probability (disease prevalence) of the condition. Health care workers are confronted with two major questions at primary care health facilities: 1) Does the child need to be referred? For which an algorithm must evaluate sensitivity and specificity in relation to the severity of disease. 2) Does the child require specific treatment (most often an antibiotic)? For which the disease prevalence of a bacterial illness needs to be considered when evaluating the sensitivity and specificity of such an algorithm.

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reduce morbidity and mortality. However if this high sensitivity comes at the cost of reduced specificity, it can result in over-referral, misallocation of limited health care resources, and excess antibiotic prescription [38]. While this concept was considered within the development of the algorithm, most predictors and models studied lacked sufficient sensitivity and specificity to appropriately meet these requirements at the primary care level, thus emphasizing the need for better predictors and models [35,38].

Once a severe condition has been excluded, restricting antimicrobial prescriptions can be more safely integrated given the lower risk of clinical failure. Understanding the pre-test probability (disease prevalence) of the disease guides us on the level of specificity needed for the corresponding predictors to be included in the algorithm. In the outpatient settings, few non-severe children above 2 months have a condition requiring antibiotics [11,27]. As such, using the principles of Bayes' theorem [43], an algorithm for a condition of low prevalence requires a higher likelihood ratio to have a similar post-test probability than a condition with a higher prevalence. Within ePOCT+, C-Reactive Protein (CRP) test is integrated in several branches of the algorithm to increase specificity/likelihood ratio when the pre-test probability of requiring antibiotics is low. However, the pre-test probability of requiring antibiotics may increase in a child with comorbidities, and therefore a lower CRP cut-off can be used to increase sensitivity and reach the same post-test probability.

d) Integrating overall clinical impression

The overall clinical impression of a healthcare worker plays an important part in the diagnostic process [44], and may sometimes better identify serious conditions compared to isolated symptoms and signs [45,46]. As blindly following CDSA recommendations runs the risk of neglecting nuanced clinical observations or patient-initiated elements, we incorporated clinical impression in the algorithm to better preserve these skills [47]. More generally, it also shows a respect and consideration for the clinician's judgment and allows the tools to be more participatory; including the clinician in the interpretation and responsibility of the decision. As such, attempts were made to combine multiple clinical elements into one question utilizing clinical impression. This approach was used to help identify children who need a referral or antibiotics, such as "Severe difficult breathing needing referral", a criteria similar to that proposed by the British Thoracic Society [48], and "well/unwell appearing child", often used in children with fever without apparent source [36,49]. Highlighting in the application that this response will result in a recommendation of referral, aims to help clinicians understand the impact of their selection, and thus improve both the sensitivity and specificity. Such composite elements reduce the number of questions prompted by the CDSA, and speeds up the consultation process; an important consideration for uptake. Nevertheless, the diagnostic and prognostic value of the overall clinical impression of primary care clinicians in LMIC settings is not well understood, and further research is needed to understand how helpful these types of elements are when integrated within ePOCT+.

Adapting and validating the medical content

ePOCT+ was first developed for Tanzania, where the prior generation of the algorithm was validated in a randomized-controlled trial [11]. Following the expansion and adaptation of the content described above, the algorithm was internally reviewed by 13 clinicians from 6 medical institutions with good understanding of CDSAs; 5 working in Tanzania, and the other 8 with experience working in LMICs. The ePOCT+ algorithm for Rwanda, Senegal, Kenya and India were then each drafted, with rounds of internal review, by small development teams composed of clinical algorithm development specialists, and national child health experts based on country-specific objectives, guidelines, and epidemiology, using the first algorithm as a scaffold.

In each country, the ePOCT+ algorithm was reviewed by a technical panel from the Ministry of Health or an independent clinical expert group (usually with Ministry of Health representatives). The panels were asked to assess the algorithm in terms of clinical validity, feasibility in primary care, scope of illnesses, and consistency with national policy and guidelines. The process of validation varied slightly in each country according to national decision-making mechanisms, but all included written feedback, individual and group meetings.

Certain algorithm branches were highlighted for group discussion; especially those with novel content, those for which significant interpretation was required from national guidelines, and any branches with queries or comments from panel members. For the algorithms with more novel content, more formal decision processes were used. In Tanzania and Rwanda a modified nominal group method was used, in which each participant one-by-one provided their opinion on the presented branch of the algorithm, followed by a group discussion and then an absolute majority vote for the final version.

Following the internal and external reviews, further modifications were made during the digitalization process, and feasibility tests, including feedback and review from end-users. For each proposed major change, the modification was communicated to the group to allow subsequent feedback and final approval by health authorities.

Digitalization of ePOCT+ and development of the medAL-suite

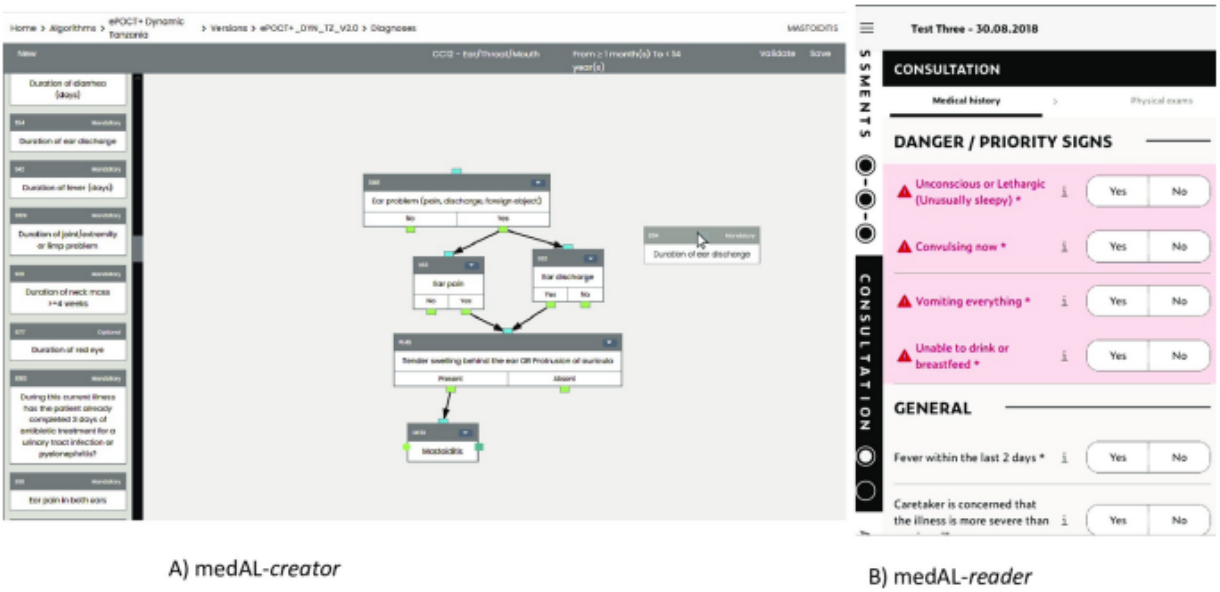
We performed a landscaping review of existing CDSA software with respect to user interface, open source, data management, ease of programming and interpretation of clinical algorithms, and operability in target health facilities. Since none of the available software packages met our requirements, we developed the medAL-suite software following the requirements of the target product profile for CDSAs [21]. medAL-*creator* allows clinical experts to design the clinical content and logic of the algorithm, while medAL-*reader* is an Android based interface to execute the algorithm to end-user clinicians (Fig 3). Both software were developed collaboratively between the clinicians, IT programmers, end-users via feedback from field tests, and health authorities from the implementation countries.

The World Health Organization (WHO) have recently proposed the SMART guidelines to provide guidance and structure to translate the narrative guidelines (Layer 1), to semi-structured "human readable" decision trees and digital adaptation kits (Layer 2), to computer/machine readable structured algorithms (Layer 3), to the executable form of the software (Layer 4), and finally dynamic algorithms that are trained and optimised to local data (Layer 5) [50]. Each "translation" between layers is prone to interpretation and error, especially when each layer is developed by different actors and continuously adapted. To reduce error in interpretation, a major feature of medAL-*creator* is to allow the "computer/machine readable" structured algorithms to be "human readable", thus merging Layers 2 and 3. medAL-*creator* features a "drag and drop" user interface and automatic terminology/code set enabling the clinicians with no programming knowledge to create and review the algorithm. medAL-*reader* is then able to automatically convert the algorithm from medAL-*creator* for use at point-of-care.

medAL-*reader*, was designed based on our previous experiences of CDSA interfaces [8,11], and expert guidance on successful strategies in order for the application to be intuitive to use with limited training, to align with normal workflows at primary health care facilities, and encourage user autonomy [21,51,52].

Validation tests and user-experience evaluations

Validation tests were performed for each diagnosis to ensure that the inputted data within medAL-*creator* were processed correctly into the expected output on medAL-*reader*. This



A) medAL-*creator* B) medAL-*reader*

Fig 3. medAL-*creator* and medAL-*reader*. A) medAL-*creator* and its "drag and drop" user interface to design the clinical algorithm. For each clinical element a description and/or photo can be included to assist the end-user using medAL-*reader*; B) medAL-*reader* the android based application to collect the medical history, exposures, symptoms, signs and tests, and then propose the appropriate diagnosis and management.

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included automated unit and integration testing, as well as automated non-regression testing by medAL-*creator*, and manual verification of medication posology for all drugs according to weight and age of the patient. All issues were reviewed by a clinical and IT team to correct the problems. While such tests are encouraged by the CDSA TPP [21], since CDSAs are not considered a "software as a medical device" by the Food and Drug Administration (FDA) [53] or European Medical Device Coordination Group [54], these tests are not legally required.

The ePOCT+ tool underwent numerous types and rounds of testing. To start, over 500 desk-based review cases focusing on user interface and analytical validation were performed by the various team members. Analytical validation tests ensured that the clinical content that was programmed in medAL-*creator* had the correct output in the medAL-*reader* application. End-user testing using fictional cases and supervised consultations concentrated on user experience, acceptability, and clinical applicability. Finally integrated testing in real-life conditions were performed where feedback was sought regularly. All user experience feedback was reviewed by a team including both clinical and IT specialists, while all clinical content modifications were approved by both the internal and external review panels.

Ethics

Activities related to the development and piloting of ePOCT+ and the medAL-suite were done within the studies of DYNAMIC and TIMCI, for which approval was given from each country of implementation. The study protocol and related documents were approved by the institutional review boards of the Ifakara Health Institute in Tanzania (IHI/IRB/No: 11–2020 and 49–2020), the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol. IX/3486 and NIMR/HQ/R.8a/Vol. IX/3583), the National Ethics Committee of Rwanda (752/RNEC/2020), the Comité National d'Ethique pour la Recherche en Santé of Senegal (SEN20/50), the University of Nairobi Ethics and Research Committee in Kenya (UON/CHS/TIMCI/

1/1), the King George's Medical College Institutional Ethics Committee in India (103rd ECM IC/P2), the Indian Council of Medical Research (2020–9753), the cantonal ethics review board of Vaud, Switzerland (CER-VD 2020–02800 & CER-VD 2020–02799), and the WHO Ethics Review Committee (ERC.0003405 & ERC.0003406). Written informed consent was obtained from all parents or guardians of children involved in the piloting of ePOCT+ and medAL-*reader*. No informed consent was obtained from health care workers involved in the development and refinement of the tools.

The exploratory analysis of predictors from the 2014 ePOCT study received approval of the study protocol and related documents by the institutional review boards of the Ifakara Health Institute and the National Institute for Medical Research in Tanzania (NIMRrHQ,R.8a,/trI'-VolI. 789), by the Ethikkommission Beider Basel in Switzerland (EKNZ UBE 15/03), and the Boston Children's Hospital ethical review board. Written informed consent was obtained from all parents or guardians.

Results

The ePOCT+ clinical algorithm and supporting evidence for each country of implementation can be found on the websites of the DYNAMIC and TIMCI studies that are implementing ePOCT+. The major features of medAL-*creator* and medAL-*reader* are summarized in the supplementary material (S4 Appendix), including the requirements defined by the CDSA target product profile (S5 Appendix).

The feasibility tests of ePOCT+ were conducted in over 200 patients in 20 health facilities, leading to numerous modifications (Table 1). The improved algorithm was then piloted with over 2000 consultations following 2 days of training and on-site support, before officially starting the clinical validation studies in the five countries of implementation.

Discussion

ePOCT+ was derived from existing evidence and clinical validation field studies from previous generation CDSAs [8,10,11]. Novel content in the algorithm compared to other CDSA include

Table 1. Example of modifications based on user-experience feedback and observations.

Issue	Description + context	Modifications
CDSA impractical in emergency situations	Child with convulsions was brought into the consultation room interrupting the current consultation. The clinician stopped using the tablet and managed the child providing the incorrect antibiotic class and dose	Emergency button integrated so that emergency management guidance can easily be accessed at any point of the algorithm.
Understanding algorithm branches	Why a patient reached a specific diagnosis was not always well understood by clinicians	To improve understanding, and to have medAL-*reader* as a learning tool, efforts were made to simply present the decision tree logic for individual diagnostic and syndromic branches of the algorithm.
Some medicines not available at health facilities due to stock-outs	Sometimes medicines recommended by national guidelines were not available	Provide alternative medicines for most conditions in case the recommended one is not available.
Misunderstanding of the labelling of some clinical elements	The labelling of some symptoms and signs were not well understood by the clinician	Modification of labelling of some elements, clarification provided in the information button, and translation to local language
Some clinical signs not measured, especially when patients are many	Many clinicians did not always measure required clinical signs (anthropometrics, temperature, respiratory rate) and could thus not continue with the algorithm	Provide options to not measure some clinical signs and rather estimate the values (with warning that this is sub-optimal) to limit clinicians being 'stuck', to discourage false information to be entered, and to provide mentorship to those not measuring these signs
No clear identification of symptoms and signs that always result in severe disease / referral	Clinicians selected variables that resulted in a severe diagnosis, parenteral antibiotics, and referral, for which the clinician did not agree with.	Elements that result in the diagnosis of a severe disease and referral are highlighted

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decision logic for young infants less than 2 months, and in some countries decision logic for children 5–15 years old, and expanded clinical content for diagnoses not included in IMCI. It is now being further validated in several large clinical studies. Following established development protocols, attempts were made to ensure a transparent development process, multi-stakeholder collaboration, and end-user feedback [21,22,55,56]. Specifically, aligning the development process of ePOCT+ and specifications of medAL-*reader* to the requirements of the Target Product Profile for CDSAs was helpful to better meet the needs of end users in terms of quality, safety, performance and operational functionality [21]. The development of medAL-*creator*, allows non-IT specialists to be able to program the clinical algorithms using a no-code, drag and drop interface, a novel solution that democratizes the development of CDSAs. This is a big advantage when compared to other CDSA tools that generally require advanced IT knowledge to review and program the code of the CDSA. Nonetheless, there are several limitations and challenges with the development process and the end-result of ePOCT+ and the medAL-*suite*, for which ongoing modifications and improvements will be required.

First, while efforts were made to improve the performance of the algorithm, there was often a reliance on clinical guidelines which may not always be founded on the best/latest/highest quality evidence, or applicable to low resource primary care settings [57,58]. Furthermore, they require significant interpretation to transform into algorithms. Digital Adaptation Kits (DAKs) to guide implementers in how to interpret narrative guidelines to transform into digital platforms are currently being developed by the World Health Organization and should help address this challenge in the future [50,59]. Often supplementary evidence was needed to complement national and international guidelines. This evidence should ideally be identified through systematic reviews [60], however those are not always feasible. Leveraging existing evidence databases as done by another CDSA may be a more feasible method to avoid biases in identifying supporting evidence [61]. Among the supporting evidence identified, there was a paucity of evidence for conditions specific to older children above 5 years, prognostic studies in the primary care setting, and diagnostic studies for conditions other than serious bacterial infection and pneumonia. Evaluating the prognostic and diagnostic value of predictors and models used in ePOCT+ during the ongoing validation studies will help to develop more efficient and better performing algorithms optimised for the target population [50,62].

A number of considerations were taken into account when digitalizing and adapting paper guidelines. Among the most important considerations were the feasibility, acceptability, reliability, and diagnostic and prognostic performance of individual clinical elements, while also considering the overall performance of the algorithms in relation to the pre-test probability of the outcome or disease, and the clinician's overall impression. Often conflicts can arise among the various factors that must be considered, which leads to difficult decisions. For example the Delphi survey among Tanzanian health care workers found that capillary refill time may not be feasible in primary health settings, however it has been found to have good prognostic value [35]. Such difficult decisions were often taken with input from clinical experts from the country of implementation. Additional training on clinical signs deemed not feasible, could potentially allow for future modifications. Another difficult decision included the option of estimating results when measurements are not possible (e,g, respiratory rate). Health care workers often do not measure respiratory rate when following paper guidelines or using a CDSA [7,19]. If the CDSA does not allow the option of not being able to measure respiratory rate then health care workers may not be able to move forward using the tool, or may enter false data if indeed respiratory rate measurement is not feasible. Allowing health care workers to estimate the value is not ideal, but allows the health care worker to at the very least visually assess respiratory rate, and provide an input in order for the algorithm to reach a diagnosis.

This data can then be used to mentor health care workers that do not measure respiratory rate. Allowing clinicians to simply indicate that the respiratory rate was not possible to measure without forcing an estimation could be an option to consider, but would complicate the decision on what diagnosis to reach when selecting this option.

Many modifications to ePOCT+ and medAL-*reader* compared to previous generation CDSAs were implemented in order to help improve uptake, addressing previously shared concerns such as limited scope, and ease of use. medAL-*reader* was specifically designed to follow normal healthcare workflows, and incorporate more input from the healthcare workers. Compared to other CDSAs, medAL-*reader* includes new functions such as an emergency button, and the ability to accept or refuse a diagnosis or treatment. The introduction of other digital tools such as electronic medical records within the same health facilities creates challenges in uptake and may result in duplication of processes. As an example, it is estimated that there are over 160 digital health or health-related systems in Tanzania [63]. While efforts are currently being made to harmonize processes so that different digital systems can complement each other rather than creating additional work, this has not yet been achieved. It is important to note, that while ePOCT+ and medAL-*reader* may address some challenges to uptake of CDSAs, there are many extrinsic and intrinsic factors that are not addressed, such as the low perceived value of following guidelines, and lack of motivation partly related to poor remuneration [16,64].

The digitalization process allows for increased complexity in the algorithm compared to paper guidelines. However, this complexity may limit the understanding by healthcare workers. Understanding how a diagnosis and treatment plan is reached is fundamental to clinical and patient autonomy, important for continued learning, and for fostering trust in any algorithm.[65–67] Efforts were made to present simple decision tree logic for each diagnosis. Nevertheless, the optimal method of presentation of algorithm branches to assure understanding by primary healthcare workers should be further explored.

Conclusion

ePOCT+ aims to improve clinical care of sick children in LMICs, notably by reducing unnecessary antibiotic prescription. We hope that the strong stakeholder involvement, the expanded scope of the clinical algorithm, and the novel software of the medAL-*suite* will result in high uptake, trust and acceptability. Widespread implementation will provide opportunities for dynamic and targeted refinements to the clinical content to improve the performance of the algorithm. We further hope that the easy-to-use platform of the medAL-*suite*, and the framework used to develop ePOCT+ will allow health authorities and local communities to be able to take ownership of ePOCT+ or their own clinical algorithm for future adaptations and developments. Future success however, is contingent on the harmonization with national health management information systems and other digital systems.

Supporting information

S1 Appendix. Prevalence of specific symptoms and diagnoses not covered in IMCI from Tanzania.
(DOCX)

S2 Appendix. Delphi survey on the reliability and feasibility of measurement of symptoms and signs.
(DOCX)

S3 Appendix. Prognostic value of predictors used in the ePOCT and ALMANACH electronic clinical decision support algorithms.
(DOCX)

S4 Appendix. Features of the medAL-*creator* and medAL-*reader software as defined by a clinical-IT collaboration with end-user feedback*.
(DOCX)

S5 Appendix. Evaluation of ePOCT+ based on the characteristics set by the target product profile for electronic clinical decision support algorithm as defined by expert consensus.
(DOCX)

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5.3. A digital health algorithm to guide antibiotic prescription in pediatric outpatient care: a cluster randomized controlled trial

Title	A digital health algorithm to guide antibiotic prescription in pediatric outpatient care: a cluster randomized controlled trial
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A digital health algorithm to guide antibiotic prescription in pediatric outpatient care: a cluster randomized controlled trial

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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, hemoglobin test, pulse oximeter and mentorship, to guide health-care 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. Over 11 months, 23,593 consultations were included from 20 ePOCT+ health facilities and 20,713 from 20 usual care facilities. The use of ePOCT+ in intervention facilities resulted in a reduction in the coprimary outcome of antibiotic prescription compared to usual care (23.2% versus 70.1%, adjusted difference −46.4%, 95% confidence interval (CI) −57.6 to −35.2). The coprimary outcome of day 7 clinical failure was noninferior in ePOCT+ facilities compared to usual care facilities (adjusted relative risk 0.97, 95% CI 0.85 to 1.10). There was no difference in the secondary safety outcomes of death and nonreferred secondary hospitalizations by day 7. Using ePOCT+ could help address the urgent problem of antimicrobial resistance by safely reducing antibiotic prescribing. Clinicaltrials.gov identifier: NCT05144763

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 human immunodeficiency virus (HIV) combined. Inappropriate and excessive prescription of antibiotics represents one of the primary contributors to 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 inappropriate[5,9–11]. Antibiotic use and AMR are projected to increase over the coming years, indicating the urgency to take

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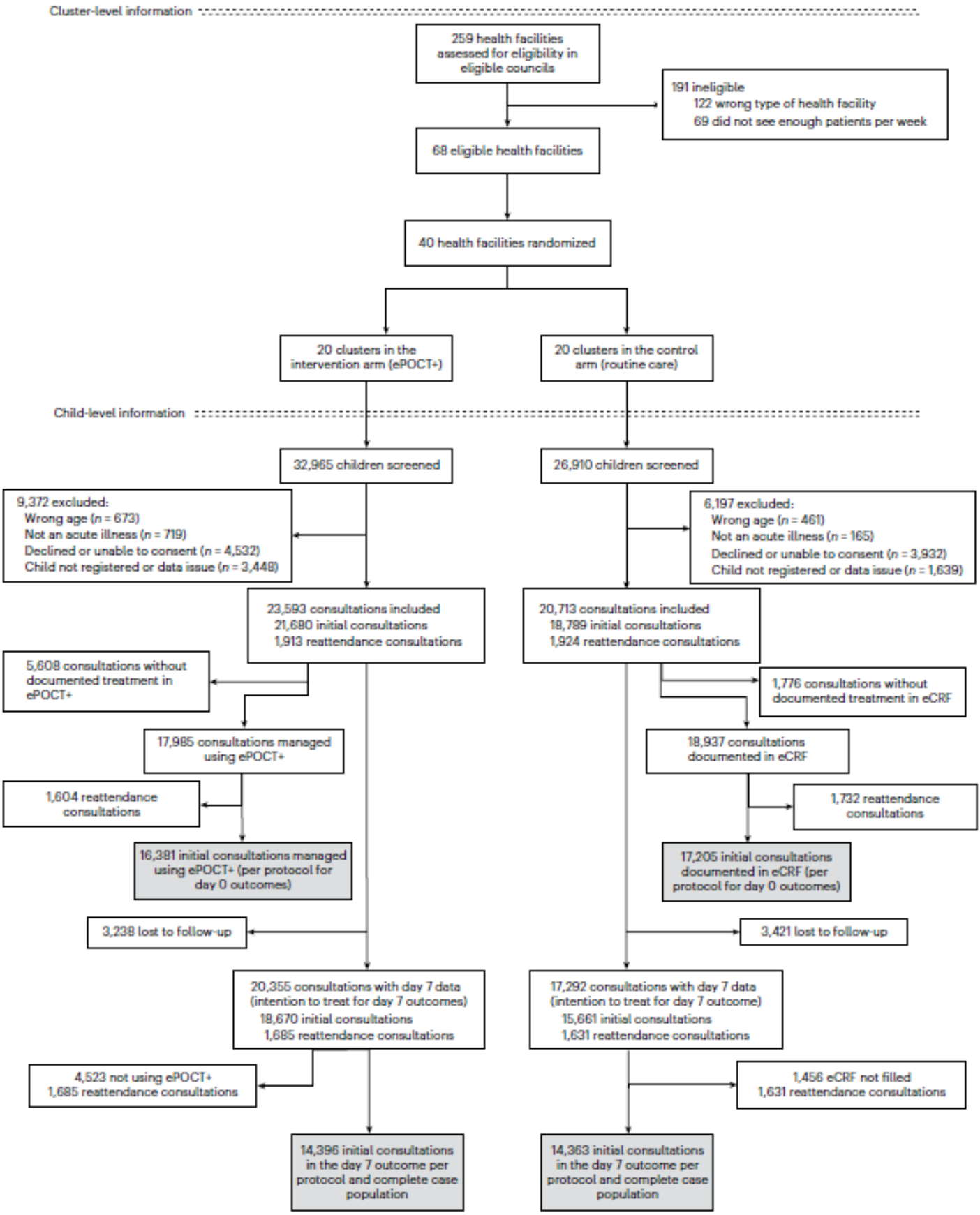

Fig. 1 | Health facility and patient flow diagram. Boxes highlighted in gray correspond to the coprimary outcome populations.

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Table 1 | Baseline characteristics of enrolled participants and health facilities

Health facilities	ePOCT+ (*n*=20)	Usual care (*n*=20)
Level of health facility, *n*		
Dispensaries	16	16
Health centers	4	4
Region, *n*		
Morogoro	12	12
Mbeya	8	8
Number of enrolled patients per health facility per month, median (IQR)	127 (101; 199)	136 (73; 163)
Service availability and readiness assessment[a]		
General Service Readiness score, % (mean±s.d.)	60.3±10.8	63.7±9.4
Pediatric score, % (mean±s.d.)	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, days, median (IQR)	583 (263; 1,202)	555 (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)
Reattendance	7.8 (1,841)	9.2 (1,899)
Referral from another health facility	0.3 (72)	0.1 (25)
Positive malaria test among those tested, % (*n*/*N*)	18.4 (1,878/10,225)	19.2 (1,803/9,378)
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)

Participant data from all enrolled patients. Values of standard deviations (s.d., 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[21].

Table 2 | Presenting complaints of infants and children under 15 years old

Presenting complaints, %	ePOCT+	Usual care
Infants <2 months	*n*=717	*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
Infants and children ≥2 months to <15 years	*n*=17,268	*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 (including burns, wounds, poison)	1.5	2.0
Other	2.1	4.2

Data from patients for whom 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.

action[12–14]. Accordingly, the World Health Organization has declared AMR as "one of the biggest threats to global health, food security and development today"[15]. In response, countries worldwide, including Tanzania, have developed national action plans on antimicrobial resistance to address this important problem[16,17].

Electronic clinical decision support algorithms (CDSAs) are digital health or mobile health tools that guide health-care providers on what symptoms and signs to assess, advise on what tests to perform, and propose the appropriate diagnoses, treatments and management[18,19]. Previous efficacy studies under controlled research conditions have shown the potential for digital CDSAs to reduce antibiotic prescription in children 2 to 59 months old[20,21]. However, many close-to-real-world studies have shown little to no reduction in antibiotic prescription[22–24]. 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[18,24,25], 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[26,27].

We developed ePOCT+, a new CDSA with point-of-care tests, to address these challenges[28]. The scope of ePOCT+ was expanded from previous versions of the CDSA[20,29] to include infants under 2 months and children up to age 14 years, and to address syndromes and diagnoses not considered by other CDSAs[30]. 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.

Result

Baseline characteristics of health facilities and patients

A total of 68 out of 259 health facilities from the participating councils met the eligibility criteria (Fig. 1). One hundred twenty-two health facilities were ineligible as they were either hospitals or private dispensary or health centers, and 69 did not see enough patients per week. A stratified random sampling process identified 40 health facilities for inclusion in the study (24 in the Morogoro region and 16 in the Mbeya region), which were randomized 1:1 to ePOCT+ (intervention) or usual care (control). Overall, 59,875 children were screened for inclusion between 1 December 2021 and 31 October 2022, and 44,306 (74%) consultations were enrolled (23,593 in ePOCT+ health facilities and 20,713 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 a mean of 1.6 consultations per patient over the duration of the study. Among those enrolled in the intervention health facilities, 17,985

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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
Nonreferred 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 (0.96; 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% (−15.4%; 12.4%)	−2.8% (−11.8%; 6.2%)	0.83 (0.51; 1.34)	0.44	0.86 (0.53; 1.40)	0.55
Unplanned reattendance 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

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. Nonreferred secondary hospitalizations by day 7 are hospitalizations at least a day after the initial consultation that were not referred by a health-care provider. Unplanned reattendance visits by day 7 are return visits between day 1 and 7 that were not proposed by the initial health-care 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, mean number of patients seen per month at the health facility) baseline characteristics. Formal adjustments were not performed for multiple testing. [a]Post hoc exploratory outcome not prespecified. [b]Denominator is based on consultations for which a primary referral was proposed and day 7 hospitalization data were ascertained, and as such may be less than the total number of primary referrals at day 0. [c]Including unplanned outpatient and hospitalized reattendance visits.

(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 electronic case report form (eCRF), and 17,292 consultations (83.5%) had day 7 outcome ascertained. Information technology (IT) problems and power outages were reported by research assistants on 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 being prevented from enrollment 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)[31]. Patients in both study arms were similar in age, sex, type of consultation and previous hospitalization (Table 1). Malaria prevalence among those tested was similar in both study arms (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 often for respiratory conditions, whereas patients 2 months and above had a similar distribution in presenting complaints (Table 2). Age, phone availability and level of health facility differed among patients with and without day 7 outcome ascertained (Supplementary Tables 1 and 2). Patients managed and not managed per protocol were similar, except for the level of health facility (Supplementary Table 3).

Primary outcomes: antibiotic prescription and clinical failure

Overall antibiotic prescription at initial consultations for the per protocol analysis was 23.2% (3,806 of 16,381) in ePOCT+ health facilities and 70.1% (12,058 of 17,205) in routine care health facilities, which corresponds to an adjusted absolute difference of −46.4% (95% CI −57.6 to −35.2) (Table 3 and Fig. 2). The adjusted analysis found a 65% reduction in the risk of prescribing an antibiotic at day 0 (adjusted relative risk (aRR) 0.35, 95% CI 0.29 to 0.43, $P < 0.001$). Using a conservative imputation analysis approach in the intention-to-treat population by considering that all patients who were not managed per protocol were prescribed an antibiotic, antibiotic prescription remained lower in ePOCT+ health facilities than in usual care, with an adjusted absolute difference of −34.2% (95% CI −42.1% to −26.4%) (Extended Data Table 1). When including reattendance cases, antibiotic prescription reduction was similar, with an adjusted absolute difference of −45.0% (95% CI −56.3% to −33.6%) (Supplementary Table 4).

The proportion of patients with clinical failure by day 7 was noninferior in ePOCT+ health facilities (3.7%, 532 of 14,396) compared to usual care health facilities (3.8%, 543 of 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 and Fig. 3). Clinical failure by day 7 was also noninferior in the intention-to-treat complete case population (Extended Data Table 1), when including reattendance cases (Supplementary Table 4) and using unadjusted analyses (Table 3 and Fig. 2).

Secondary and exploratory clinical safety outcomes

There were no significant differences in the proportion of patients who died, were subjectively worse or, were hospitalized after the day of the initial consultation without a referral (nonreferred secondary hospitalization), all hospitalizations by day 7 or unplanned reattendance visits (Table 3). There was however a significant reduction in

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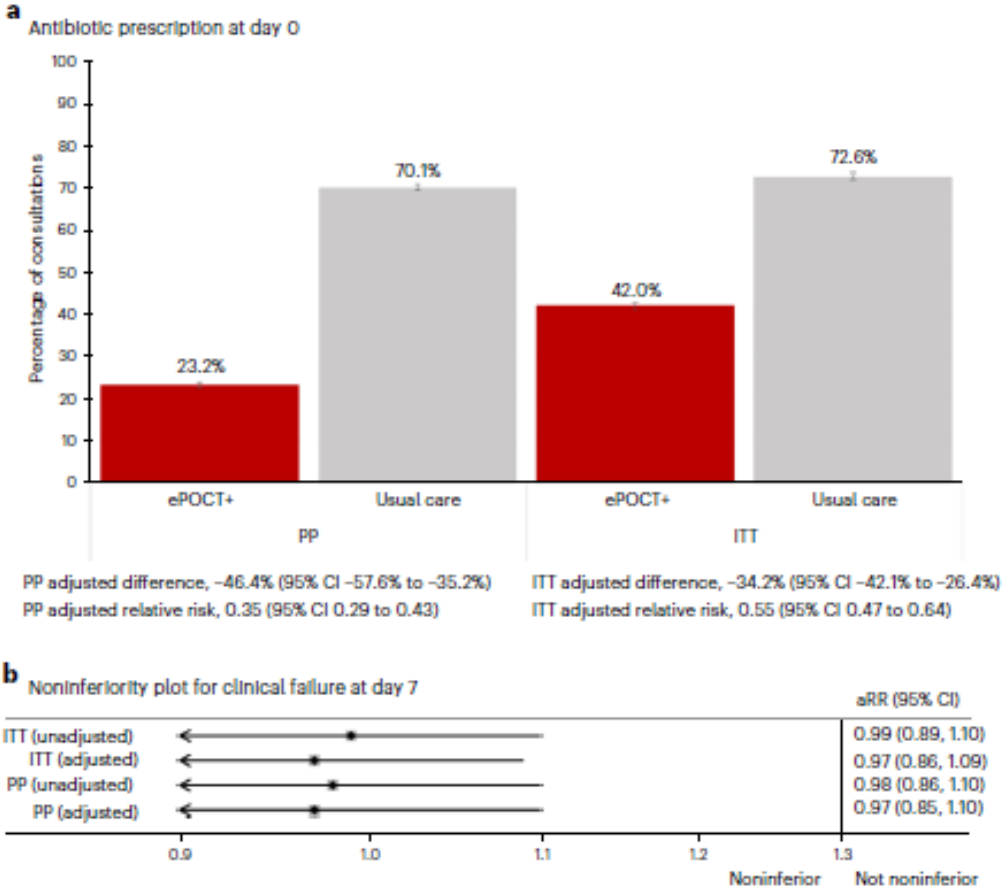

Fig. 2 | Coprimary outcomes. a, Proportion of antibiotic prescription in ePOCT+ and usual care health facilities; data are presented as the point estimate and unadjusted 95% confidence intervals. Sample sizes are as follows: PP ePOCT+ clusters $n = 16,381$, PP usual care clusters $n = 17,205$, ITT ePOCT+ clusters $n = 21,680$, ITT usual care clusters $n = 18,789$. **b**, Relative risk of day 7 clinical failure between ePOCT+ and usual care health facilities, with noninferiority prespecified as an adjusted relative risk of <1.3. Noninferiority plot shown on a logarithmic scale. ITT, intention to treat; PP, per protocol; aRR, adjusted relative risk.

unplanned reattendance visits by day 7 in unadjusted analyses. The proportion of patients who died (0.1%) or were hospitalized (1.0%) was low in both study arms. Results in the intention-to-treat population and when including reattendance visits were similar (Extended Data Table 1 and Supplementary Table 4).

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 in both study arms (7.1% versus 7.2% in intervention versus 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, whereas no change was found in usual care facilities (Supplementary Fig. 1).

Referral and hospitalizations

Health-care providers identified 3.6% (582 of 15,799) of cases as having a severe diagnosis in ePOCT+ facilities compared to 2.6% (453 of 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 (Supplementary Table 5).

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% to −60.9%) and the 2–59-month age group (absolute difference −48.9%, 95% CI −49.9% to −47.9%) (Fig. 3 and Extended Data Table 2). Antibiotic prescription was reduced by at least 25 percentage points in all prespecified subgroups, with the smallest reduction found in infants under 2 months old (absolute difference −25.5%, 95% CI −30.3% to −20.6%). Among post hoc subgroup analyses, patients with a positive malaria test had a lower reduction in antibiotic prescription between ePOCT+ and usual care (adjusted absolute difference −18.8%, 95% CI −25.1% to −12.6%) (Extended Data Table 2). Young infants less than 2 months old had the largest reduction in day 7 clinical failure (aRR 0.61, 95% CI 0.37 to 1.00; $P = 0.05$) (Fig. 3 and Extended Data Table 3).

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 close-to three-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

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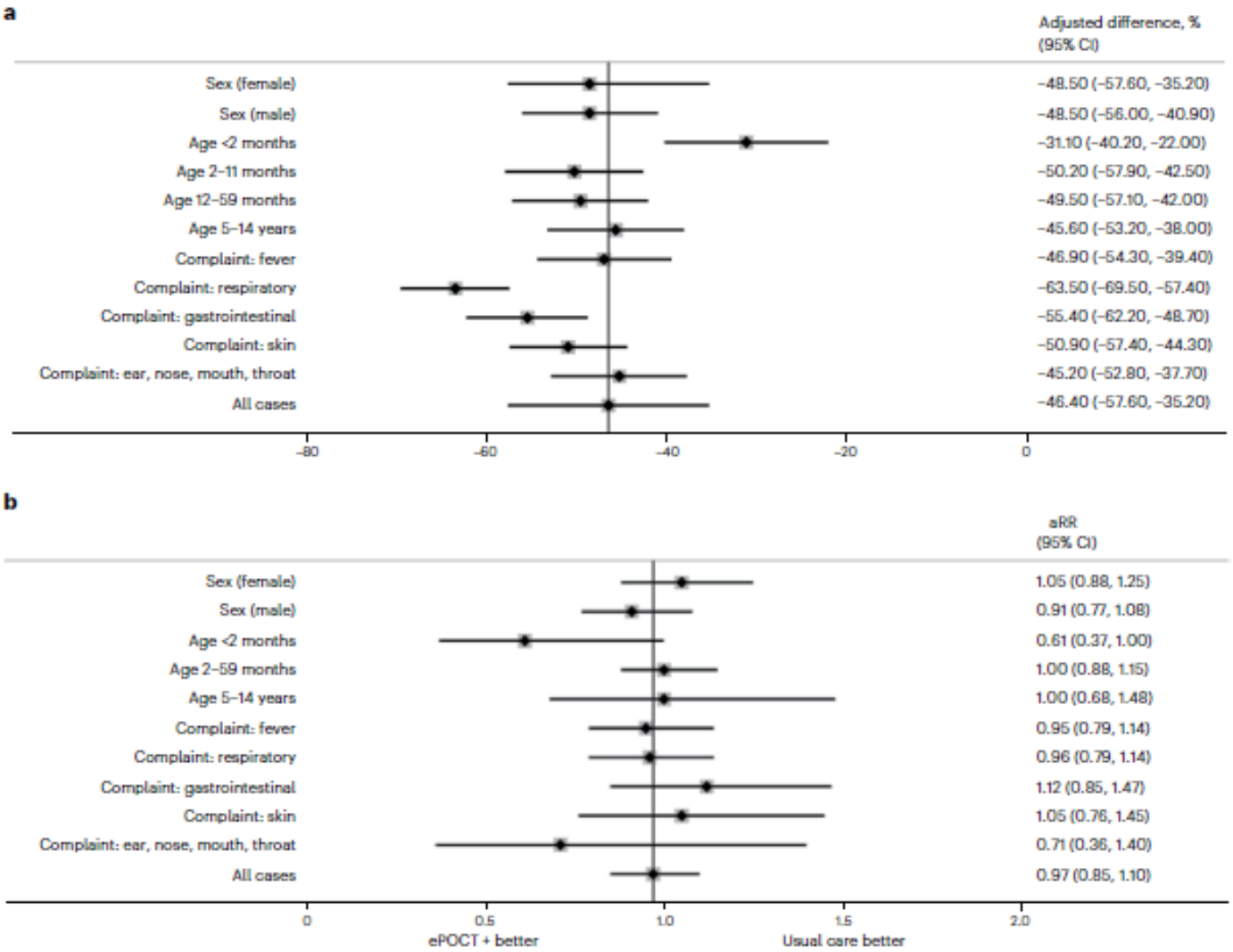

Fig. 3 | Antibiotic prescription and clinical failure by sex, age group and main complaints. a, Data are presented as adjusted differences with 95% CI of day 0 antibiotic prescription between ePOCT+ health facilities and usual care health facilities. All data are from the per protocol population in initial consultations. Sample sizes for each subgroup are found in Extended Data Table 2. **b**, Data are presented as adjusted relative risk with 95% CI of clinical failure in ePOCT+ compared to usual care health facilities. All data are from the per protocol and complete case population among initial consultations. Sample sizes for each subgroup are found in Extended Data Table 3.

did not increase in intervention facilities. Such findings align with Tanzania's National Action Plan to reduce antibiotic use[17] and are in line with the Tanzania digital health strategy to improve quality of care[32].

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[20,21,33]. However, the results differ from other studies evaluating CDSAs implemented in routine health programs in Nigeria, Afghanistan, Burkina Faso and South-Africa, and in a controlled study setting in Uganda, which found smaller and even no reduction in antibiotic prescription[22–24,34,35]. 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 C-reactive protein (CRP), not included in the Integrated Management of Childhood Illness (IMCI)[28]. 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[20]. Other differences that may explain the divergent results include (1) differences in the supportive training and mentorship provided, (2) disease epidemiology (notably malaria prevalence) and (3) health-care provider skills and adherence. The extent of the impact on antibiotic stewardship in our study is also greater than that observed in other antibiotic stewardship studies that included one single intervention rather than an intervention package[36,37]. ePOCT+ integrates multiple proven antibiotic stewardship interventions together, including clinical decision support[20,21,33], the use of point-of-care CRP tests[38], pulse oximeter[39] and continuous quality improvement mentorship support with data feedback to health-care providers utilizing benchmarking of health facilities[40,41].

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[38]. Similarly the proportions of children who died, were hospitalized without referral or had unplanned reattendance visits were not higher. Whereas previous CDSA studies were able to demonstrate significant reductions

in clinical failure, the current trial was not powered to do so[20,21,23]. Nonetheless, the greatest benefit on clinical cure compared to usual care was observed in the subgroup of infants aged under 2 months, important results given that this population represents more than 50% of mortality in children under 5 years old[42].

Although the present findings are encouraging, it is important to note that nearly 25% of patients were not managed using ePOCT+ in the intervention arm. Lower uptake of the tool could reduce the positive impact of antibiotic stewardship as seen in the lower reduction in antibiotic prescription in the intention-to-treat (ITT) population. It is reasonable to assume that not all health providers use the digital tool to manage all patients, just as health providers do not consult the IMCI paper chartbook every time they see a patient. Indeed CDSAs have been found to improve adherence to IMCI guidelines[23,24,43,44], nonetheless many challenges in adherence to paper guidelines remain for digital tools, notably low motivation, lack of on-site mentoring and cognitive overload[45,46]. The use of electronic medical record (EMR) systems in some health facilities may also explain poor uptake, as some providers were expected to input clinical data in ePOCT+, the EMR and a paper log, prolonging the consultation time. Integration of clinical decision support within the EMR system instead of separate standalone systems could help and is currently being explored. In addition to harmonization of digital health tools, numerous other factors must be considered and are currently being evaluated in order for ePOCT+ and similar tools to be adequately scaled up in Tanzania and other countries. They include a better understanding of why health providers did not use ePOCT+ and how the clinical algorithms of ePOCT+ can be further improved, how health providers can be better supported to use the digital tools, the impact of benchmarking and mentoring dashboards, cost and greenhouse gas emission analyses, and acceptance by patients and community members.

Our study possesses several strengths that contribute to its robustness. First, we employed a cluster randomized controlled study design, which was adequately powered to assess noninferiority of clinical failure. Second, 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 centers. Moreover, our study employed comprehensive patient inclusion criteria that were designed to be inclusive. By incorporating these 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 health-care provider, an approach often used in pragmatic trials[47,48]. When using a conservative imputation analysis approach in the ITT population considering that all patients for which treatment was not documented were considered to have been prescribed an antibiotic, ePOCT+ still reduced antibiotic prescription considerably (Extended Data Table 1). Second, despite multiple phone calls and home visits, 15% of cases were lost to follow-up, consistent with data from similar studies (13–25%)[49–51]. 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 situations. To show an effect on more severe outcomes such as secondary hospitalization, death or even clinical failure at day 14 or 28 would require a very large sample size owing to the rarity of the event at the primary care level. Further complicating assessment of these severe outcomes are the 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, hemoglobin, pulse oximeter) and mentorship support informed by clinical practice data, safely and substantially reduced antibiotic prescription in sick children less than 15 years of age 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 content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02633-9.

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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 five councils in the Mbeya and Morogoro region, with a total population in those councils of 1,701,717 (ref. 52). Two councils were semiurban (Mbeya city and Ifakara Town councils), whereas the three others were rural (Mbeya, Ulanga and Mlimba district councils). Overall 42.8% of the Tanzanian population is less than 15 years old[53]. The prevalence of malaria in febrile children aged 6–59 months is 5.8% in the Morogoro region and 3.4% in the Mbeya region[54]. In accordance with the Tanzanian national clinical guidelines, all febrile patients should be tested for malaria using a rapid diagnostic test at the health facility of contact[55]. HIV prevalence among children less than 15 years old is 0.5% in both regions[56]. Health care for acute illnesses at government or government-designated primary health facilities is free of charge for children under 5 years, including the cost of medications such as antibiotics. For patients older than 5 years, health-care expenses are charged to the patient, unless they have a health insurance plan (around 10% of Tanzanians)[57].

First-level health facilities included in the DYNAMIC Tanzania study include dispensaries and health centers with the latter distinguished by several characteristics. Health centers are characterized by multiple outpatient consultation rooms, potential presence of medical doctors, occasional small inpatient wards and a broader array of diagnostic and therapeutic capabilities compared to dispensaries.

Participants

Primary care health facilities (dispensaries or health centers) were eligible for inclusion if they performed on average 20 or more consultations per week with children aged from 2 months to 5 years, 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, whereas medical doctors provide care occasionally at health centers. 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[58].

Infants and children between 1 day old and 15 years old 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 (for example HIV, tuberculosis, malnutrition) or for routine preventive care (for example 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 (to include more health facilities in the higher malaria transmission area). In addition, to include a representative sample of health centers compared to dispensaries, four health centers 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 with the list of all eligible health facilities and performed computer-generated sampling and randomization. Intervention allocation by the study team was only shared with study investigators in Tanzania once all council leaders had confirmed the participation of their selected health facilities. The nature of the intervention did not allow for masking of the intervention to health-care providers, patients or study implementers.

Intervention

The intervention consisted of providing ePOCT+ with the supporting IT infrastructure, C-reactive protein (CRP) semiquantitative lateral flow test, hemoglobin point-of-care tests (and hemoglobinometer if not already available), pulse oximeter, training and supportive mentorship (Extended Data Fig. 1). If unavailable in health facilities, materials to perform laboratory tests such as prickers, cotton swabs, gloves and alcohol were provided. The decision to perform tests (malaria, CRP, hemoglobin, pulse oximeter), like all clinical symptoms and signs, is determined by the clinical algorithm behind ePOCT+, and prompted to the health-care provider when required. The health-care provider can decide not to follow the recommendations of ePOCT+ as they see fit. CRP point-of-care rapid tests and hemoglobin point-of-care tests were integrated as per usual laboratory procedures (that is, in health facilities where point-of-care tests are usually performed and interpreted in the laboratory by a laboratory technician, tests were performed in the laboratory; in health facilities where tests are usually done in the consultation room, they were done by the health-care provider). The development process and details of the ePOCT+ CDSA and the medAL-reader Android-based application used to deploy ePOCT+ have been described in detail previously[28]. In summary the clinical algorithm of ePOCT+ is based on previous-generation CDSAs (ALMANACH and ePOCT)[20,29], international and national clinical guidelines, and input from national and international expert panels, and was adapted based on piloting and health-care provider feedback[28]. Mentorship by the implementation team included visits to health facilities every 2 to 3 months and communication by phone call or group messages three to four 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 health-care providers to compare their antibiotic prescription, uptake and other quality-of-care indicators with other health facilities[59]. 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 eCRFs. 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 power. In addition, weighing scales, mid-upper arm circumference bands and thermometers were provided to health facilities for both study arms if not already available. Health-care providers from both intervention and control health facilities received equivalent clinical refresher training based on the 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 08:00 and 16:00 on weekdays. If eligible, demographic information was collected and entered in the eCRF (ePOCT+ for intervention health facilities and eCRFs for usual care facilities within the data collection system medAL-reader). Health-care 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 whether an oral or systemic antibiotic was prescribed, and whether 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. Health-care 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 behavior 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 five attempts. The home visits were performed by the research assistants enrolling patients from the same health facility, and 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 were recorded using REDCap web for phone calls and REDCap mobile application for home visits.

Outcomes

The coprimary outcomes measured at the individual patient level included: (1) antibiotic prescription at the time of the initial consultation as documented by the health-care provider (superiority analysis); and (2) clinical failure at day 7 defined as 'not cured' and 'not improved', or unscheduled hospitalization as reported by caregivers (noninferiority analysis). Secondary outcomes include unscheduled reattendance visits at any health facility by day 7, nonreferred secondary hospitalization by day 7, death by day 7 and referral for inpatient hospitalization at initial consultation. Additional antibiotics prescribed on subsequent days following the initial consultation were not part of the coprimary outcome of antibiotic prescription; instead this is captured by phone call on day 7, where all patients are assessed for whether additional medication was taken after the initial consultation, and compared between study arms as an exploratory outcome. Given patients' and caregivers' difficulty in distinguishing antibiotics from other medications[60,61], we could not reliably assess antibiotic intake based on the caregiver's report; the outcome thus looked at all medications, rather than antibiotics specifically. The intervention was deemed a success if ePOCT+ was noninferior in terms of clinical failure and reduced antibiotic prescription by at least 25%. Prespecified additional outcomes are outlined in the statistical analysis plan.

Sample size

The sample size was calculated for testing noninferiority of the clinical failure outcome given that it would require a higher sample size than for the antibiotic prescription coprimary outcome. We assumed a cluster size of 900 patients per health facility (mean of 150 patients per month per health facility multiplied by 6 months, the minimum duration of the study) based on routine data within the national 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 noninferiority 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, owing 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 (Supplementary Information Note 1). The study team prespecified 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[62], and baseline characteristics hypothesized to be associated with the outcome, imbalances between arms and imbalances between characteristics among patients for whom day 7 data were 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-cluster and between-cluster effects to account for confounding by cluster[63–65]. 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 and absolute differences were estimated based on the computed marginal probabilities of the conditional probabilities[66,67]. Formal adjustments were not performed for multiple testing, as adjustments would likely be overly conservative given that the outcomes are not all independent[68], and variable selection was not based on statistical tests of significance[69]. No adjustment for baseline characteristics or for within-health-care-facility correlations was used for the calculation of crude confidence intervals for relative risk and absolute differences.

Noninferiority was determined if the upper limit of the 95% CI of the 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 reattendance 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 complaint, skin problem, ear, nose and throat problem). All analyses were performed using Stata v.16 and v.17 (ref. 70).

Inclusion and 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) and 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 (statistical analysis plan also found in Supplementary Information Note 2). 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 health-care providers involved in our similar trials in Tanzania[20,21,33]. In addition, previous work from Tanzania was used to guide the design of the study and to develop ePOCT+, and other work from Tanzania was taken into account in the citations for this manuscript[32,45,46]. ePOCT+ and the medAL-suite was developed collaboratively by an international group of digital and global health

experts from Tanzania and other LMICs[28]. Specifically a Tanzanian clinical expert group including representatives designated by the Ministry of Health made the final decision on clinical content, and primary care level health providers gave important feedback to develop and improve ePOCT+, including a Delphi survey among 30 Tanzanian health providers[28]. Over 100 community engagement meetings with over 7,000 participants were conducted before and during the study, including numerous meetings with Community and Regional Health Management Teams in the Mbeya and Morogoro regions of Tanzania.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

De-identified data can be found at https://doi.org/10.5281/zenodo.8043523, including case, patient and health facility identification number, study arm allocation, baseline characteristics and all outcomes.

Code availability

The code for the medAL-reader application used to collect data entered by health providers (including demographic, clinical, diagnosis, prescription and referral data of the consultations) can be found at https://github.com/Wavemind/liwi-medal-reader.

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Author contributions

R.T., A.V.K., K.K., N.N., H. Masanja and V.D.A. were responsible for study design. R.T., A.V.K. and V.D.A. came up with the statistical analysis plan. R.T. was responsible for data curation. R.T. and P.T. carried out the formal analysis. K.K., N.N., H. Masanja and V.D.A. acquired funding. R.T., G.K., L.B.L., A.V.K., S.R., C.M., G.A., M.J., I.E.M., P.A. and H. Mhagama carried out the investigation. A.V.K., L.B.L., C.M., S.R. and V.F. were responsible for project administration. R.T., A.V.K., L.B.L., C.M., S.R., V.F., J.T., N.N., H. Masanja. and V.D.A. supervised the project. R.T. wrote

the original draft of the paper. R.T., G.K., L.B.L., A.V.K., S.R., C.M., G.A., M.J., I.E.M., P.A., H. Mhagama., A.V., V.F., J.T., G.L., M.-A.L.P., K.K., P.T., N.N., H. Masanja. and V.D.A. wrote, reviewed and edited the final paper. R.T. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests
The authors declare no competing interests.

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Extended Data Fig. 1 | Description of ePOCT+ and supportive mentorship intervention. The intervention included the provision of the ePOCT+ Clinical Decision Support Algorithm (CDSA), C-Reactive Protein & Hemoglobin point-of-care tests, and pulse oximeter. The use of these additional tests and tools are proposed within the ePOCT+ CDSA. The intervention also included the sharing of quality of care indicators within dashboards which allowed healthcare providers to see their performance compared to other health facilities. Finally mentorship support in the form of messages, phone calls, and visits were conducted to answer questions and support the use of ePOCT+. Both intervention and control health facilities received equivalent Integrated Management of Childhood Illness (IMCI) training, and Information Technology (IT) support. If required the health facilities also received a weighing scale, mid-upperarm circumference (MUAC) band, and thermometer.

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Extended Data Table 1 | Primary, secondary and exploratory outcomes in initial cases in the intention-to treat population

	ePOCT+, % (*n/N*)	Usual Care, % (*n/N*)	Adjusted Difference (95% CI)	Crude Relative Risk (95% CI)	p-value	Adjusted relative risk (95% CI)	p-value
Primary outcomes							
Antibiotic prescription at day 0*	42% (9,105/21,680)	72.6% (13,642/18,789)	-34.2% (-42.1%; -26.4%)	0.58 (0.57; 0.59)	<0.001	0.55 (0.47, 0.64)	<0.001
Clinical failure by day 7	3.8% (708/18,670)	3.8% (599/15,661)	-0.1% (-0.6%; 0.3%)	0.99 (0.89; 1.10)	0.88	0.97 (0.86, 1.09)	0.60
Secondary outcomes							
Death by day 7	0.1% (9/18,670)	0.1% (11/15,661)	-0.0% (-0.1%; 0.0%)	0.69 (0.28; 1.66)	0.40	0.59 (0.21; 1.65)	0.31
Exploratory outcomes							
Subjectively worse by day 7**	0.3% (60/18,670)	0.3% (44/15,661)	0.0% (-0.1%; 0.1%)	1.14 (0.78; 1.69)	0.50	1.08 (0.73; 1.62	0.69
Hospitalizations by day 7**	1.0% (189/18,670)	0.9% (145/15,661)	0.2% (-0.1%; 0.6%)	1.09 (0.88; 1.36)	0.42	1.26 (0.86; 1.85)	0.25
Additional medication taken after initial consultation up to day 7	7.0% (1,301/18,473)	7.2% (1,109/15,512)	-0.7% (-1.9%; 0.4%)	0.99 (0.91; 1.06)	0.70	0.90 (0.77; 1.06)	0.21

Secondary and exploratory outcomes that rely on data collected on day 0 are not shown as this information is not available for all ITT patients (non-referred secondary hospitalizations by day 7, completed referral, primary referrals at day 0). All outcomes that rely on day 7 outcomes are complete case analyses. Adjusted relative risks and differences were estimated using a random effects logistic regression model adjusting for clustering (health facility, and patient), and individual and health facility baseline characteristics that were available for all ITT cases (age, sex, availability of phone, council of health facility, level of health facility, average number of patients seen per month at the health facility). Formal adjustments were not performed for multiple testing. *Considering that all cases that were not managed per protocol were prescribed an antibiotic; **Post-hoc exploratory outcomes

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Extended Data Table 2 | Stratified subgroup analysis for antibiotic prescription at D0 in initial consultations in the per protocol population

Subgroup	ePOCT+, % (n/N)	Usual Care, % (n/N)	Adjusted Difference (95% CI)	Crude relative risk (95% CI)	p-value	Adjusted relative risk (95% CI)	p-value
All cases	23.2% (3,806/16,381)	70.1% (12,058/17,205)	-46.4% (-57.6%; -35.2%)	0.33 (0.32; 0.34)	<0.001	0.35 (0.29; 0.43)	<0.001
Sex (female)	23.4% (1,971/8,429)	70,1% (6,194/8,835)	-48.5 (-56.0%; -40.9%)	0.33 (0.32; 0.35)	<0.001	0.32 (0.28; 0.38)	<0.001
Sex (Male)	23.1% (1,835/7,952)	70.1% (5,864/8,370)	-48.5% (-56.1%; -40.9%)	0.33 (0.32; 0.34)	<0.001	0.32 (0.27; 0.38)	<0.001
Age < 2 months	34.7% (233/672)	60.2% (524/871)	-31.1% (-40.2%; -22.0%)	0.58 (0.51; 0.65)	<0.001	0.56 (0.47; 0.66)	<0.001
Age 2-11 months	18.0% (891/4,949)	70.0% (3,817/5,456)	-50.2% (-57.9%; -42.5%)	0.26 (0.24; 0.27)	<0.001	0.28 (0.23; 0.34)	<0.001
Age 12-59 months	23.5% (2,056/8,743)	70.7% (6,068/8,579)	-49.5% (-57.1%; -42.0%)	0.33 (0.32; 0.35)	<0.001	0.31 (0.26; 0.37)	<0.001
Age 5-14 years	31.0% (626/2,017)	71.7% (1,649/2,299)	-45.6% (-53.2%; -38.0%)	0.43 (0.40; 0.46)	<0.001	0.40 (0.34; 0.47)	<0.001
Complaint : Fever	27.3% (2,654/9,729)	74.9% (7,083/9,458)	-46.9% (-54.3%; -39.4%)	0.36 (0.35; 0.38)	<0.001	0.38 (0.32; 0.44)	<0.001
Complaint : Respiratory	18.6% (1,450/7,809)	80.7% (6,784/8,407)	-63.5% (-69.5%; -57.4%)	0.23 (0.22; 0.24)	<0.001	0.25 (0.21; 0.29)	<0.001
Complaint : Gastrointestinal	22.9% (884/3,867)	70.6% (2,707/3,837)	-55.4% (-62.2%; -48.7%)	0.32 (0.30; 0.34)	<0.001	0.30 (0.26; 0.35)	<0.001
Complaint : Skin	29.5% (598/2,028)	67.84% (1,390/2,049)	-50.9% (-57.4%; -44.3%)	0.43 (0.40; 0.47)	<0.001	0.39 (0.34; 0.45)	<0.001
Complaint : Ear, Nose, Mouth, Throat	40.7% (175/430)	80.0% (304/395)	-45.2% (-52.8%; -37.7%)	0.53 (0.47; 0.60)	<0.001	0.48 (0.42; 0.56)	<0.001
Phone number available[a]	22.9% (3,115/13,583)	70.8% (10,034/14,168)	-48.3% (-55.8%; -40.8%)	0.32 (0.31; 0.33)	<0.001	0.33 (0.28; 0.38)	<0.001
Phone number not available [a]	24.7% (691/2,798)	66.6% (2,024/3,037)	-49.2% (-56.9%; -41.4%)	0.37 (0.35; 0.40)	<0.001	0.31 (0.26; 0.37)	<0.001
Health Facility (Dispensary) [a]	23.3% (3,047/13,078)	71.5% (10,262/14,346)	-48.2% (-49.3%; -47.2%)	0.33 (0.32; 0.34)	<0.001	0.32 (0.27; 0.38)	<0.001
Health Facility (Health Centre) [a]	23.0% (759/3,303)	62.8% (1,796/2,859)	-39.8% (-42.1%; -37.6%)	0.37 (0.34; 0.39)	<0.001	0.34 (0.22; 0.55)	<0.001
Low malaria risk health facility [ab]	21.2% (2,004/9,469)	70.6% (7,668/10,864)	-41.9% (-56.4%; -27.4%)	0.30 (0.29; 0.31)	<0.001	0.41 (0.29; 0.58)	<0.001
High malaria risk health facility [ab]	26.1% (1,802/6,912)	69.2% (4,390/6,341)	-55.7% (-67.7%; -43.6%)	0.38 (0.36; 0.39)	<0.001	0.24 (0.16; 0.35)	<0.001
Positive malaria test[a]	18.6% (347/1,870)	31.4% (565/1,802)	-18.8% (-25.1%; -12.6%)	0.59 (0.53; 0.67)	<0.001	0.37 (0.27; 0.50)	<0.001

Adjusted relative risks and differences were estimated using a random effects logistic regression model adjusting for clustering (health facility and patient), and individual and health facility baseline characteristics (age, sex, complaints, phone availability, council of health facility, level of health facility, average number of patients seen per month at the health facility). Formal adjustments were not performed for multiple testing. [a]Post-hoc exploratory subgroup analyses [b]Malaria risk defined as per IMCI: Low risk = <5% malaria positivity rate in febrile children; High risk > = 5% malaria positivity rate in febrile children

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Extended Data Table 3 | Subgroup analysis for clinical failure at day 7 in the per protocol, complete case population among initial consultations

Subgroup	ePOCT+, % (n/N)	Usual Care, % (n/N)	Adjusted Difference (95% CI)	Crude relative risk (95% CI)	p-value	Adjusted relative risk (95% CI)	p-value
All cases	3.7% (532/14,396)	3.8% (543/14,363)	-0.1% (-0.5% ; 0.4%)	0.98 (0.87; 1.10)	0.70	0.97 (0.85; 1.10)	0.59
Sex (female)	3.6% (270/7,375)	3.5% (258/7,360)	-0.2% (-0.5%; 0.8%)	1.04 (0.88; 1.23)	0.61	1.05 (0.88; 1.25)	0.59
Sex (Male)	3.7% (262/7,021)	4.1% (285/7,003)	-0.3% (-1.0%; 0.3%)	0.92 (0.78; 1.08	0.30	0.92 (0.77; 1.09)	0.31
Age < 2 months	4.1% (24/590)	6.5% (46/708)	-2.2% (-4.4%; -0.0%)	0.63 (0.39; 1.01)	0.05	0.61 (0.37; 1.00)	0.05
Age 2-11 months	4.9% (207/4,222)	4.5% (200/4,469)	0.3% (-0.6%; 1.2%)	1.10 (0.91; 1.32)	0.35	1.07 (0.88; 1.31)	0.49
Age 12-59 months	3.3% (253/7,717)	3.4%(243/7,145)	-0.1% (-0.7%; 0.5%)	0.96 (0.81; 1.15)	0.68	0.97 (0.81; 1.16)	0.70
Age 5-14 years	2.6% (48/1,867)	2.7% (54/2,041)	-0.0% (-1.0%; 1.0%)	0.97 (0.66; 1.42)	0.88	0.99 (0.67; 1.47)	0.98
Complaint : Fever	3.0% (259/8,561)	3.1% (240/7,842)	-0.2% (-0.8%; 0.4%)	0.98 (0.82; 1.16)	0.79	0.95 (0.79; 1.14)	0.58
Complaint : Respiratory	3.4% (233/6,896)	3.6% (253/7,042)	-0.2% (-0.8%; 0.5%)	0.94 (0.79; 1.12)	0.49	0.96 (0.79; 1.16)	0.64
Complaint : Gastrointestinal	4.0% (133/3,326)	3.6% (114/3,160)	0.4% (-0.6%; 1.4%)	1.11 (0.87; 1.42)	0.41	1.12 (0.85; 1.47)	0.41
Complaint : Skin	5.6% (101/1,808)	5.2% (89/1,712)	0.2% (-1.2%; 1.7%)	1.07 (0.81; 1.42)	0.61	1.05 (0.76; 1.45)	0.76
Complaint : Ear, Nose, Mouth, Throat	3.8% (15/398)	5.7% (19/336)	-1.5% (-4.5%; 1.5%)	0.67 (0.34; 1.29)	0.23	0.71 (0.36; 1.40)	0.32
Phone number available[a]	4.2% (504/12,146)	4.2% (513/12,211)	-0.0% (-0.6%; 0.5%)	0.99 (0.88; 1.11)	0.84	0.99 (0.86; 1.12)	0.83
Phone number not available[a]	1.2% (28/2,250)	1.4% (30/2,152)	-0.2% (-1.0%; 0.5%)	0.89 (0.54; 1.49)	0.66	0.85 (0.50; 1.43)	0.54
Health Facility (Dispensary) [a]	3.3% (384/11,735)	3.5% (425/11,996)	-0.1% (-0.6%; 0.4%)	0.92 (0.81; 1.06)	0.25	0.97 (0.84; 1.12)	0.71
Health Facility (Health Centre) [a]	5.6% (148/2,661)	5.0% (118/2,367)	-0.0% (-1.4%; 1.4%)	1.12 (0.88; 1.41)	0.36	1.00 (0.75; 1.33)	0.99
Low malaria risk health facility[ab]	3.9% (328/8,345)	4.3 (396/9,114)	-0.0% (-0.7%; 0.7%)	0.90 (0.78; 1.04)	0.17	1.00 (0.83; 1.20)	0.99
High malaria risk health facility[ab]	3.4% (204/6,051)	2.8% (147/5,249)	-0.2% (-1.4%; 1.0%)	1.20 (0.98; 1.48)	0.08	0.94 (0.69;1.29)	0.70
Positive malaria test[a]	1.8% (29/1,573)	2.1% (30/1,409)	-0.7% (-2.4%; 1.0%)	0.87 (0.52; 1.44)	0.58	0.81 (0.48; 1.36)	0.42
Negative malaria test[a]	3.7% (274/7,434)	3.2% (208/6,424)	0.7% (-0.1%; 1.5%)	1.14 (0.95; 1.36)	0.15	1.20 (0.97; 1.49)	0.09
No malaria test performed[a]	4.5% (309/6,826)	4.8% (386/8,006)	-0.9% (-1.6%; -0.1%)	0.94 (0.81; 1.09)	0.40	0.80 (0.67; 0.97)	0.02
Region: Morogoro[a]	3.4% (357/10,484)	3.6% (330/9,282)	0.0% (-0.7%; 0.7%)	0.96 (0.83; 1.11)	0.57	1.00 (0.82; 1.23)	0.97
Region: Mbeya [a]	4.5% (175/3,912)	4.2% (213/5,081)	-0.3% (-1.6%; 1.0%)	1.07 (0.88;1.30)	0.52	0.93 (0.69; 1.25)	0.63

Clinical failure by day 7 defined as 'not cured' and 'not improved', or unscheduled hospitalization as reported by caregivers. Adjusted relative risks were estimated using a random effects logistic regression model adjusting for clustering (health facility and patient), and individual and health facility baseline characteristics (age, sex, complaints, availability of phone, council of health facility, level of health facility, average number of patients seen per month at the health facility) but omitting the variable as an adjustment variable in the model for the subgroup analyzed. Formal adjustments were not performed for multiple testing. [a]Post-hoc exploratory subgroup analyses [b]Malaria risk defined as per IMCI: Low risk = <5% malaria positivity rate in febrile children; High risk > = 5% malaria positivity rate in febrile children

6. Discussion

The present thesis sought to evaluate how to improve quality of care and reduce antibiotic prescription using digital clinical decision support algorithms at primary care level health facilities for the management of sick children less than 15 years old. More specifically this thesis outlined new evidence on the improved identification of febrile children at risk of severe disease, developed a novel clinical decision support algorithm based on a new software platform for implementation in primary care settings and finally evaluated the impact of this digital tool (ePOCT+) on antibiotic prescription and clinical outcome.

This work contributes to helping improve quality of care and reduce antibiotic prescription at primary care level health facilities using digital tools. However, careful interpretation is required considering limitations and additional needs in order for this evidence to be successfully applied.

6.1. Identification of children with severe disease

The systematic review in chapter 5.1 identified individual predictors and models to identify febrile children at risk of severe outcome. Findings from this study, helped inform the clinical algorithms for ePOCT+ described in chapter 5.2, can help in the development of other clinical algorithms and guidelines, and help clinicians assessing febrile children. In addition, prognostic data collected in the frame of the cluster randomized-controlled trial described in chapter 5.3 also provide insight into how to better identify children at risk of severe illness. If well implemented prognostic models and individual predictors with proven efficacy can reduce morbidity and mortality, while allowing for better allocation of limited healthcare resources (McDonald et al, 2018; Molyneux et al, 2006). Integrating such evidence at the primary care level is complex and must consider a number of elements.

Appropriateness of predictors for primary care level health facilities

The appropriateness of individual predictors to integrate within clinical guidelines must be assessed in regard to the setting of implementation. Some individual predictors may not be routinely collected, or even feasible to assess depending on the context. In chapter 5.2 (supplementary material) I describe a Delphi survey we performed among 30 Tanzanian health care providers that found that some clinical predictors are not appropriate for primary care level health facilities in Tanzania. Specifically, we looked at the feasibility, acceptability and reliability of different clinical predictors, and found that capillary refill time, the assessment of cool peripheries, and weak and fast

pulse, were not appropriate for primary care level health facilities, despite being helpful predictors to identify children with severe disease. While subjective, appropriateness of predictors considered results of the Delphi survey on feasibility, acceptability, and reliability. As such models identified in the review, such as, AQUAMAT (George et al, 2015; von Seidlein et al, 2012), FEAST-PET (George et al, 2015), Kwizera models (Kwizera et al, 2019), PEWS (Parshuram et al, 2009), and SICK model (Kumar et al, 2003), could not be integrated at primary care. While specific training could be provided in order to allow current health providers to reliably and feasibly assess for such signs, this must be considered within the global training curriculum of health providers and weighed in importance based on prognostic value and incidence.

Other individual predictors may simply not be feasible at primary level health facilities based on available human and material resources and costs. Examples identified in the review include oxygen saturation, blood pressure, and laboratory tests such as lactate, glucose, and potassium. As such, models identified in the review that would not be applicable for primary care settings include AQUAMAT (George et al, 2015; von Seidlein et al, 2012), FEAST-PETaL (George et al, 2015), ELSHOUT (Elshout et al, 2015), PEWS (Parshuram et al, 2009), q-SOFA (Seymour et al, 2016), q-SOFA-L (van Nassau et al, 2018), SCOTT (Scott et al, 2020), SICK (Kumar et al, 2003), and SIRS (Goldstein et al, 2005). Nonetheless, some have demonstrated high prognostic value (Robinson et al, 2019), which merits evaluation on cost-effectiveness and pertinence of such tests for integration at the primary care setting. The introduction of point-of-care tests can also help address challenges related to healthcare provider training and reliability. Indeed, clinical scores integrating point-of-care tests often perform better than with clinical signs alone (Keitel et al, 2019a). As such the scale-up of diagnostics at the primary care level is an essential process that may increase the feasibility of integrating important predictors at the primary care level (Fleming et al, 2021).

Need and challenge of prognostic studies at the primary care level

The aforementioned limitations reflect the hospital level bias of studies evaluating the prediction of severe disease. Indeed only 2/18 studies identified in the systematic review, and 765/24 530 (3.1%) of children were from the primary care level. More prognostic studies at the primary care level is essential to better help guide clinical guidelines at this level of care. Not only would such studies better provide evidence on predictors more frequently available or more feasible/reliable to be assessed by the health providers at the primary care setting, but it would better contextualize the performance of such predictors in this setting. Indeed, the performance of predictors may differ substantially when evaluated in a hospital setting compared to primary care level setting.

The lack of primary care level prognostic studies may not be solely due to a lack of researchers interested in this setting, but likely also to the complexity of conducting research at this level. Primary care level health facilities generally see much less severe patients compared to hospitals, as such one would have to include sometimes more than 20 times more primary care health facilities than hospitals in order to include the same number of patients with the sought after endpoint of death or prolonged hospitalization. Coordinating data collection in numerous health facilities, that are often in more rural and hard to reach locations is certainly more challenging than at a centralized hospital. Severe outcome definitions often include criteria such as prolonged hospitalization, in-hospital mortality, admission to intensive care units, or progression to organ dysfunction, which requires hospital data. Linking this data with primary care level health facility data further complicates data collection and interpretation. Finally, severe outcomes and predictors of severe disease are rare at primary care level health facilities. In the cluster randomized trial described in chapter 5.3, we found only 20/34,331 (0.1%) of patients in 40 primary care level health facilities died by day 7, and only 334/34,331 (1.0%) were hospitalized. Developing a prognostic model based on the widely used criteria of 10 events per variable (Moons et al, 2015), would mean that only 2 variables could be included from a dataset of 40 health facilities over 11 months. Developing a prognostic model including 5 variables would thus require around 28 primary care facilities collecting data over one year. External validation of such a model, for which the general rule of thumb requires at least 100 events (Collins et al, 2016; Vergouwe et al, 2005), would again require 56 health facilities over one year. Finally, if one were to evaluate the benefit on mortality reduction in a prospective individual or cluster randomized trial, the studies would require respectively 392 and 1,238 health facilities recruiting patients over one year (table 2).

Table 2: Sample size requirements for different type of studies evaluating mortality at primary care level health facilities*

Research study type	Sample size requirement	Required sample size	Number of health facilities over one year
Prognostic model development predicting mortality	10 Events Per Variable x 5 variables	50,000	28
External validation of a prognostic model predicting mortality	100 events	100,000	56
Individually randomized controlled trial	Demonstrate a 20% reduction in mortality (80% power, alpha 0.05	705,760	392

Cluster Randomized-Controlled trial**	Demonstrate a 20% reduction in mortality (80% power, alpha 0.05)	2,228,400	1,238

*Assuming mortality of 0.1%, mean cluster size of 150/month = 1800/year based on the DYNAMIC TZ cluster RCT (Tan et al, 2023)

**Assuming intracluster correlation coefficient of 0.001, and coefficient of variation of cluster size of 0.7

Mortality may thus not be the most relevant clinical outcome for the primary care level. Indeed mortality is a useful prognostic outcome in order to identify those requiring admission to intensive care units, at the primary care level the clinical question pertains more to the necessity of hospitalization or not. As such less severe outcomes that remain somewhat objective could include persistent fever (Elshout et al, 2015), prolonged hospitalization (van Nassau et al, 2018), and secondary hospitalization (Barbara et al, 2013). While previous attempts at developing clinical prediction models with less severe outcomes resulted in low predictive performance, most were done in high-income settings (Chandna et al, 2021b). Evaluating predictive performance and derivation of a clinical model to predict severe disease using data from the DYNAMIC project, may help fill this important clinical gap (Miauton et al manuscript in preparation).

Opportunities and challenges for better clinical prognostic data

Digital health tools such as CDSAs and electronic medical records (EMRs) provide an opportunity for addressing the dearth of clinical prognostic data at the primary care level. The documentation of clinical symptoms, signs, and test results of primary care consultations can be collected in a more standardized manner, ensuring consistent and comprehensive collection of information, enabling more accurate prognostic assessments. Using data from the DYNAMIC Tanzania study described in chapter 5.3, and data from other studies using ePOCT+, we are in the process of evaluating the prognostic value of clinical predictors and developing a clinical model to predict severe illness.

However, to fully harness the potential of digital health tools for developing and validating clinical prognostic models, it is crucial to link data from primary care health facilities, and data from hospitals and/or death certificate. This is addressed in part within Tanzania's Digital Health Investment Road Map, but not yet implemented (Government of Tanzania, 2017). In the DYNAMIC Tanzania study presented in chapter 5.3, we collected such data via phone call 7 days after their initial consultation. While this is possible in a clinical study context, collection of this data through routine mechanisms via data linkage would be ideal. Despite the benefits, linking such data

introduces legal and ethical challenges. Patient privacy and data security must be protected to ensure compliance with healthcare regulations and maintain patient trust. Data sharing agreements, consent mechanisms, and stringent data anonymization techniques must be implemented to address these concerns. Moreover, interoperability among various digital health tools and systems is necessary to facilitate the seamless exchange of information while maintaining data integrity and privacy. This introduces a significant amount of work and coordination that should be considered at the start of any digital health project in order to succeed. Specifically, data governance frameworks should be planned with established roles, responsibilities, and processes for data linkage and maintenance, in addition to standardization of data formats, terminologies, and protocols.

6.2. Lessons learnt and future improvements based on the development and implementation of ePOCT+

Chapter 5.2 described the development of the CDSA ePOCT+ based on the medAL-suite digital platform for CDSAs. At the time of conception ePOCT+ was piloted in just over 2000 patients in 20 health facilities. Since then ePOCT+ and the medAL-suite has been used for over 300,000 consultations in Tanzania, Rwanda, Kenya, Senegal and India (Beynon et al, 2023), including over 16,000 consultations within the cluster randomized-controlled trial in Tanzania described in chapter 5.3. Here I will describe lessons learnt and future perspectives on improving ePOCT+.

Improving ePOCT+ algorithms and uptake through use logs of health providers

The WHO's **S**tandards-based, **M**achine-readable, **A**daptive, **R**equirements-based, and **T**estable (SMART) Guidelines provide advice on the digitalization of clinical guidelines (Mehl et al, 2021). The framework of these guidelines is structured around knowledge 'layers' based on previous work by Boxwala et al (Boxwala et al, 2011). The different layers of the SMART guidelines include the clinical/narrative guidelines (Layer 1), semi-structured "human readable" decision trees and digital adaptation kits (Layer 2), computer/machine readable structured and agnostic algorithms (Layer 3), the executable form of the software (Layer 4), and finally dynamic algorithms trained and optimized to local data (Layer 5). The final layer is also reflected within the principles of digital development in order to be data driven (Waugaman, 2016).

In line with these principles, in addition to the other principles for digital development; "Be collaborative", "Design with the user", and "Reuse and Improve", the next section will explore how findings based on the experience of ePOCT+ since development could help improve ePOCT+ and other CDSAs for better antibiotic stewardship, improved quality of care, and improved clinical outcome. A number of approaches can be used to understand how ePOCT+ was used and how it can

be improved. First, qualitative and mixed-method approaches can be used by conducting in-depth interviews, focus group discussions, and surveys; second, evaluate use logs to understand how the use of ePOCT+ can inform modifications; and third, evaluate uptake in association to implementation.

One method ePOCT+ sought to integrate health providers' judgment in order to render the tool more participative, was to allow them to "accept" or "reject" diagnoses reached by the algorithm, and to indicate if they truly referred a patient. This allows health providers to integrate other clinical information not incorporated in the algorithms, while allowing data analysis to understand which diagnoses are rejected more often. This data could help identify which sub-algorithms require modifications.

A preliminary analysis from ePOCT+ use logs from the cluster randomized-controlled trial described in chapter 5.3 combined with in-depth interviews and surveys, found three main group of diagnoses that were rejected at high frequency (*Manuscript in preparation).* The first, are diagnoses related to malnutrition such as complicated or uncomplicated severe acute malnutrition, or very low weight-for-age. To reach these diagnoses, a child must meet specific objective anthropometric measures based on z-scores or absolute measures in the case of mid-upper arm circumference (MUAC), sometimes in combination with clinical signs. These algorithms are in line with IMCI and training provided, as such it is indeed surprising that such diagnoses would be highly rejected. In-depth interviews found that health providers rejected these diagnoses for a number of reasons. First, many acknowledged that anthropometric measurements were not always measured the same day of evaluation, as such if indicating past measurements or estimated measurements, there is a possibility of a false diagnosis of malnutrition. Indeed it is very common for health providers in primary health facilities to not measure anthropometric measures, so not surprising that many used past or estimated measures. Second, health providers felt there was a discrepancy in terms of the anthropometric measurements of malnutrition, and their visual assessment. Such an approach has been found to be less accurate (Hamer et al, 2004; Mogeni et al, 2011), and results in worse clinical outcomes (Tan et al, 2020). Third, there was sometimes a misunderstanding of malnutrition diagnoses, such as the difference between complicated and uncomplicated severe acute malnutrition.

Another group of diagnoses frequently rejected were severe diagnoses that would require referral, including diagnoses such as severe pneumonia, very severe disease (IMCI danger signs), and complicated severe acute malnutrition. The rationale for rejection of severe diagnoses and rejection of referral to hospitals are many. One reason could be related to cases of false positives, for which

the algorithm may have identified the child as having a severe disease; however the reality may be that it is not a true severe case, and the child does not truly need to be hospitalized. Within the cluster randomized trial described in chapter 5.3 agreement to referral for hospitalization by ePOCT+ was low, healthcare providers only referred 20.5% (119/582) of children for whom ePOCT+ recommended a referral. However clinical failure in cases for which ePOCT+ proposed a referral that was rejected by the healthcare provider compared to cases where the referral was accepted were similar (4.6% vs 4.3%). Health providers may thus be correctly rejecting referral and severe diagnoses. The systematic review on predictors of severe disease described in chapter 5.1, supports this theory, for which it was found that the specificity of IMCI danger signs were relatively poor. In addition, the incorporation of health provider clinical gestalt or overall impression often helps identify children who indeed do not require referral (Meredith et al, 2019; Van den Bruel et al, 2012). These types of rejections may be helpful to avoid over-referral of patients to conserve limited health resources. Future work to identify how algorithms can be adapted in order to avoid over-referral, while maintaining a minimum sensitivity to ensure the algorithms are safe should be pursued.

Another reason for a high proportion of rejection of severe diagnoses may be due to the socio-economic and health system challenges of referring a child to a hospital. Such rejections could be due to refusal by patients/caregivers, and/or health providers perceived hesitancy/aversion of patients to be hospitalized (Chandna et al, 2021a). While care for children under 5 years is often provided for free in most low- and middle- income countries, there are many additional costs that are not free, especially in those hospitalized. This was most recently demonstrated in randomized trials in Nigeria, Democratic Republic of Congo, and Uganda, where they found the use of pre-referral rectal-Artesunate increased mortality compared to parenteral Artesunate, due to incomplete referral of patients receiving rectal Artesunate (Hetzel et al, 2023). Similar challenges have been found in attending health consultations in patients with HIV, where food and fare were major barriers (Hodgson et al, 2014). Better understanding on why health providers and patients/caregivers reject severe diagnoses and/or referral through qualitative analyses could help identify how these challenges can be addressed.

Finally, a number of diagnoses may have been rejected due to misunderstanding of the algorithm. While efforts were made to train health providers on the use of ePOCT+, it was not possible to review every single diagnosis. Diagnoses such as “Suspected malaria”, “Suspicion of Tuberculosis”, and “Prevention and Screening”, are likely examples of diagnoses that were misunderstood. In-depth interviews confirmed this hypothesis, where when asked why some of these diagnoses were rejected, it was often clear that the goal/intention of the diagnosis was not understood (*Manuscript*

in preparation). For some problems the problem may be due to inappropriate labelling of diagnoses, while in other situations it may be due to inadequate training.

In all situations, better understanding on rejection of diagnoses and referrals can help improve ePOCT+ and subsequently improve uptake of ePOCT+, improve resource allocation by better identifying sick children who truly require hospitalization, and improve adherence to guidance.

Data driven improvements for improved quality of care: example of diagnostic models

The abundance of granular data collected via the use of CDSA have great potential to improve clinical care, as each symptom, sign, test result, diagnosis and treatment plan is documented as independent variables. In chapter 5.1, improvements to ePOCT+ and generating new evidence based on data collected from CDSAs was discussed in the context of prognosis, notably better identifying severe disease. In addition to developing new evidence and clinical models using clinical outcome data, data driven evaluations could help the development or evaluation of diagnostic models. Such analyses can help improve ePOCT+ and clinical practice more widely.

The development and evaluation of clinical models requires an objective reference standard to act as the "gold standard". In the case of ePOCT+, the use of laboratory tests can act as useful reference standards for certain diagnoses. For example C-Reactive Protein (CRP) is used to distinguish bacterial versus viral pneumonia, hemoglobin to identify anemia, and malaria rapid diagnostic test for malaria.

The use of ePOCT+ in the cluster randomized trial described in chapter 5.3 found that the use of a point-of-care hemoglobinometer increased the proportion of children with mild/moderate and severe anemia. These results however come at an increased monetary cost, and increased greenhouse gas emissions (Karlen et al. Manuscript in preparation). Evaluating the predictive value of other clinical signs in identifying anemia based on hemoglobin values, could thus help improve the identification of anemia without the use hemoglobin measurement. While previous efforts have shown the limited value of clinical signs such as pallor to detect anemia, most previous studies have been limited to the hospital setting, and smaller sample sizes (Chalco et al, 2005), justifying the value of such analyses within the ePOCT+ dataset.

Distinguishing bacterial versus viral pneumonia is challenging with radiographic infiltrates often used as a reference standard for bacterial pneumonia despite its limited predictive value (Rees et al, 2020). However, x-rays are rarely available in primary care level health facilities. CRP has been shown to be a relatively good predictor of radiologic pneumonia (Erdman et al, 2015). Within the

DYNAMIC Tanzania cluster randomized controlled trial dataset, CRP data could thus be used as a reference standard to explore the predictive value of clinical variables, or to develop a new model to predict bacterial pneumonia.

Finally, the DYNAMIC Tanzania and Rwanda dataset can also be used to validate previously derived models. Using malaria test results, we evaluated the accuracy of the IMCI malaria algorithm in low risk areas (defined by IMCI as <5% malaria prevalence in febrile children age 2 to 59 months). Our analysis found that the IMCI strategy of only testing for malaria in children with fever without an obvious cause of fever or recent travel had a sensitivity of 27.0% (Cattaneo et al. Manuscript in preparation). Results that have important implications for Ministries of Health deciding on national adaptations to IMCI, and to the WHO evaluating changes to IMCI.

Understanding the impact of implementation measures on uptake and adherence to ePOCT+

The implementation of ePOCT+ within the DYNAMIC Tanzania cluster RCT included mentorship activities including: regular monitoring calls, health facility visits, and the use clinical dashboards which allowed health providers to compare their performance compared to other health facilities (also known as "Benchmarking"). Such mentorship activities are similar to what is done with other CDSAs including ALMANACH in Nigeria (Schmitz et al, 2022), and IeDA in Burkina Faso (Sarrassat et al, 2021). The use of benchmarking has been shown to improve antibiotic stewardship strategies at the primary care level in some high-income countries (Gulliford et al, 2019; Hallsworth et al, 2016; Schwartz et al, 2021), with little to no impact in other high-income settings (Aghlmandi et al, 2023; Hemkens et al, 2017; Marwick et al, 2022), and little to no studies in LMICs (Willmington et al, 2022). Understanding the overall impact of the ePOCT+ CDSA compared to the impact of mentorship activities of ePOCT+ (including clinical dashboards), in the form of a cluster randomized-trial, will be important to understand whether such mentorship activities are required when implementing CDSAs such as ePOCT+. More specifically this could inform us if such mentorship activities and clinical dashboards help increase uptake, reduce antibiotic prescription, and improve quality of care.

Scale-up and uptake of ePOCT+: mobilizing government support and ownership

One of the most important factors to be considered for scale-up and uptake of tools such as ePOCT+ for routine use in primary care level health facilities is government ownership and support. Such support is required for all aspects of implementation, digital health harmonization and integration, and wide-scale implementation through local government actors for IT system installation, training and on-going mentorship of health providers, and monitoring and evaluation on the outputs and

outcomes. The example of the Integrated e-Diagnostic Approach (IeDA) CDSA, which is implemented in 86% of primary care health facilities in Burkina Faso by a collaboration between the Ministry of Health of Burkina Faso and the non-governmental organization Terre Des Hommes, provides good framework on how government ownership can be achieved. The scale-up of IeDA has been a long endeavor involving stakeholder mapping to assure all essential stakeholders are involved in the project, the development of a multi-stakeholder steering committee, and successful funding acquisition led by the government (Lampariello & Ancellin-Panzani, 2021). Lampariello et al. notably highlight the need for multi-sectorial engagement not limited to the health sector, and the identification of local champions that have political weight and interest to be able to push for wide scale implementation of the CDSA. With over 160 digital health tools in use in Tanzania, the Tanzanian government is actively trying to coordinate, harmonize and limit the digital tools being implemented in primary care health facilities (Watts, 2020). This strategy was outlined within the Tanzania National Digital Health Strategy 2019-2024, where the government specifies how they want to take control in a coordinated and interoperable manner (Tanzania Ministry of Health, 2019). As such government support, acceptance and ownership will likely be the deciding factor on the future of ePOCT+ and similar tools.

Expanding the scope of ePOCT+

Drawing from the lessons learned from past generation CDSAs, a prominent modification introduced in ePOCT+ was its broadened scope. Notably, ePOCT+ expanded it demographic scope to include young infants less than 2 months, and older children 5 to 15 years old. Furthermore it expanded the range of syndrome and diagnoses. This extension in age coverage allowed for further improvements to quality of care and antibiotic stewardship in these new age groups. While the expanded scope of diagnoses we hope increases uptake as it meets the need of health providers as often requested. Embracing a similar expansion in the scope of ePOCT+ and other CDSAs to include adolescents and adults would help meet an unmet need, further improving quality of care and antibiotic stewardship. Indeed, only one CDSA that managed acutely sick adolescents and adults was identified by two recent structured and systematic reviews (Agarwal et al, 2021; Keitel & D'Acremont, 2018). This study was however limited to managing only three conditions – fever, diarrhea, and respiratory problems (Gautham et al, 2015).

6.3. Reflexivity statement

I am a Swiss, Canadian, Malaysian, bi-racial (White-Asian), heterosexual cisgender male, educated and raised in high-income countries (Canada and Switzerland). I recognize that such a status comes with privilege, and puts me in the group of the oppressor in our patriarchal, racist and unequal society. As a bi-racial individual, I have been racialized as Asian, and thus understand the multifaceted ways in which racial identity can shape one's experiences and opportunities. While I have faced discrimination due to my Asian "race", I also acknowledge the advantages and privileges that come with being identified as white.

My personal identity and status in the group of the "oppressor" is of particular relevance in the context of the work of this PhD, categorized as "Global Health" or "Tropical Medicine" research. Racism, colonialism, and post-colonialism are all firmly imbedded concepts in the historical roots of research practices in low- and middle- income countries, and continues to be perpetrated today (Birn, 2014; Hirsch, 2021; Kim et al, 2019; Kwete et al, 2022). During my research in Tanzania, I have very likely perpetrated, and facilitated such structures, inadvertently upholding inequities and reinforcing colonial narratives.

I stand committed to self-reflection and continuous education, understanding that acknowledging my privilege, and the role I play in such structures as only the first step towards the decolonization of research in global health and more widely research in low- and middle- income countries. In line with this commitment it is important for me to acknowledge the personal gain, recognition, and career progression, I have benefited from the research I have conducted within these structures.

Initial drafts of this reflexivity statement included efforts done by our research group and more specifically what I have done to limit/fight against the racist and colonial structures of global health. However it is important to recognize that even well-intentioned efforts can inadvertently perpetuate harmful dynamics. Furthermore, focusing on past actions or limited accomplishments, can merely perpetuate a sense of complacency. As such, I will only concentrate on future actions.

Based on the work of Khan et al. and Costello et al. (Costello & Zumla, 2000; Khan et al, 2021) I specifically commit to the following concepts in order to limit my role in perpetuating inequities and contributing to the decolonization of global health:

- Engage in early, meaningful, and cooperative engagement with researchers and beneficiaries from the country of implementation in all stages of global health research projects
- Ensure ownership of research projects by researchers from LMICs
- Direct resources and employment opportunities to LMICs

- Support training opportunities for collaborators from LMICs
- Direct resources towards sustainability and generalizability of research findings
- Assure opportunity for research outputs by collaborators from LMICs
- Cite and promote research produced by LMIC researchers

7. Conclusion

The development of the ePOCT+ clinical decision support algorithm integrated multiple clinical guidelines, considering the latest evidence on the prognostic value of clinical signs from a systematic review, and health care provider feedback on usability, user experience, and needs. Evaluated in a cluster randomized trial in 40 primary care health facilities in Tanzania, ePOCT+ and its implementation package significantly reduced antibiotic prescription without compromising clinical cure. Such findings are encouraging and helps provide close to real-world evidence on the benefit of digital clinical decision support algorithms for antibiotic stewardship. If scaled, ePOCT+ could truly help tackle the urgent public health problem of bacterial antimicrobial resistance.

The systematic review on predictors of severe disease in febrile children outlined helpful predictors that should be considered in future clinical algorithms to assure safety and performance. Nonetheless the lack of studies from primary care settings is a limitation that needs to be addressed.

The development of ePOCT+ took a rigorous approach to improve usability, uptake and safety. Such an approach complemented by the recent SMART guidelines by the WHO could help inspire the development of other CDSAs. Nonetheless findings from the pragmatic cluster randomized trial demonstrates that uptake was not optimal. One known limitation was the limited age scope, which means some patients can be managed using ePOCT+, while other patients managed using paper guidelines. As such future expansion of clinical algorithms to manage adolescents and adults would be beneficial. Understanding the reasons for lower uptake, and adherence will be important, evaluating not only individual factors, but also systemic internal and external factors that may influence this.

The significant reduction of antibiotic prescription and non-inferior clinical outcomes are indeed measures of quality of care, nonetheless further investigations are required to better understand the impact on specific quality of care measures. Furthermore the specific impact on the mentorship package including clinical dashboards, and the specific impact of point-of-care diagnostic tests compared to the use of ePOCT+ alone are needed. Such findings can help refine future implementation strategies and help public health stakeholders strategize scale-up. The future success of ePOCT+ and similar digital health strategies depends on the handover and eventual ownership of the digital health tool by the Ministry of Health. Only then can the harmonization and integration of ePOCT+ within the digital health landscape in primary care level health facilities be achieved.

8. Recommendations

- Malnutrition, hypoxia, altered consciousness, and makers of acidosis and poor peripheral perfusion are good clinical predictors of severe disease that should be considered in clinical guidelines and algorithms when evaluating a sick child
- Careful interpretation is required when using prognostic data from the hospital setting for implementation at the primary care / community setting, notably by considering reliability and feasibility of clinical predictors, availability of diagnostic tests and tools, and pre-test probability of severe disease
- More evidence is required on how best to identify severe disease in febrile children from the primary care level, including the use of novel inflammatory marker diagnostic tests.
- Recognizing the large sample sizes required to identify severe disease in settings of low prevalence, novel approaches to collecting data including large scale collaborations and the use of digital health tools, in addition to more appropriate primary care level clinical outcomes are required.
- Data governance frameworks, data standardization, and coordination of digital health tools can help optimize the collection of data in order to generate findings that will be helpful for clinicians and public health experts to improve the health of patients.
- Multi-stakeholder engagement from multiple sectors is important at all stages of development of CDSAs to facilitate handover and ownership by Ministry of Health
- Further investigations are needed to understand the added value of diagnostic tests integrated in ePOCT+, and whether clinical models can adequately predict their results, to reduce the monetary and greenhouse gas emission cost of individual point-of-care tests.
- Future CDSAs should also help manage sick adults and adolescents in addition to children, to further reduce antibiotic prescription and improve quality of care at primary care health facilities.

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10 Curriculum Vitae

Lausanne, Switzerland; 02 October 2023

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MD, FMH Internal Medicine

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Education / Qualifications:

Ongoing **PhD in Clinical epidemiology**, Swiss Tropical and Public Health Institute, Basel, Switzerland
Thesis: Clinical Decision Support Algorithm for the improved management of sick children

2019 **Medical Doctorate**, University of Lausanne, Lausanne, Switzerland
Thesis: Severe malnutrition subgroup analysis of the ePOCT RCT

2014 **Bachelor (2011) and Master (2014) of Medicine**, University of Lausanne, Lausanne, Switzerland

2007 **Honors Bachelor of Health Sciences,** University of Ottawa, Ottawa, Canada

Professional Experience:

Apr 2023 – Ongoing (50-60%)
Attending / Head of the Migration Health Unit, Unisanté, University of Lausanne, Switzerland; Department of Vulnerable and Social Medicine
Activities: Patient care of asylum seekers of the canton of Vaud, Supervision of chief residents and residents (medical doctors) and nurses, Organization and coordination of clinical activities. Research related to health equity and migration health.

May 2018 – Ongoing (50-100%)
Research physician, Unisanté, University of Lausanne, Switzerland; Digital and Global Health Unit
Activities: Development, implementation, and analysis of the ePOCT+, clinical decision support algorithm, evaluated in a cluster RCT in Tanzania. Other research related to global health.

July 2021 - Ongoing (10-20%)
Consultant, World Health Organization (via SwissTPH since Aug 2023), Switzerland, Iraq and Cameroon
Activities: Support development of clinical content for the digitalization of IMCI into an electronic clinical decision support algorithm. Contribute to design, implementation, and pilot methodology. Work with Ministries of Health (Iraq and Cameroon) to adapt clinical algorithms to reflect national guidelines and needs.

November 2014 – October 2019 (100%)
Resident clinician, Internal Medicine
Rotations: Emergency medicine, internal medicine, infectious diseases, tropical medicine, general medicine, cardiology, pneumology, paediatrics, research

August 2007 – August 2009 (100%)
Tanzania Field Coordinator, Canada Africa Community Health Alliance (CACHA)
Activities: Coordination of projects in Tanzania. Mission-lead (2 missions) and logistics for medical missions in Tanzania, Benin, Gabon, and Uganda

January 2009 – Ongoing
Co-founder, first president, and advisor

METIS (Student Movement Working Against Health Inequities) – Switzerland & Tanzania
Activities: Creation of the by-laws, structure and development of projects working to improve access to health of vulnerable populations in Switzerland and abroad

Language Proficiency:

Language	Reading	Speaking	Writing
English	Native	Native	Native
French	Advanced	Advanced	Advanced
Spanish	Intermediate	Intermediate	Intermediate
Swahili	Basic	Intermediate	Basic

Professional Titles:

2019 Internal Medicine Board certification: Swiss Medical Association (FMH)
2019 Certificate of Travel Medicine: International Society of Travel Medicine

Society Membership:

1. American Society of Tropical Medicine and Hygiene
2. Swiss Medical Association (FMH)
3. International Society of Travel Medicine
4. Swiss Society of Tropical Medicine and Parasitology
5. British Society for Antimicrobial Chemotherapy

Grants:

- **Ambizione – Swiss National Science Foundation – August 2023**
    - Principal investigator (CHF 878,439)
- **Foster interuniversity initiatives and collaborations – Swiss School of Public Health – May 2023**
    - Co-leader (CHF 25,000)

Publications:

- **Tan, Rainer**, Kavishe, G., Luwanda, L. B., Kulinkina, A. V., … Ntinginya, N., Masanja, H. & D'Acremont, V. (2023) A digital health algorithm to guide antibiotic prescription in pediatric outpatient care: a cluster randomized controlled trial. *Nature Medicine*.
- Beynon, F., Guérin, F., Lampariello, R., Schmitz, T., **Tan, Rainer,** Ratanaprayul, N., . . . Keitel, K. (2023). Digitalizing Clinical Guidelines: Experiences in the Development of Clinical Decision Support Algorithms for Management of Childhood Illness in Resource-Constrained Settings. *Global Health: Science and Practice*.
- Beynon, F., Salzmann, T., Faye, P. M., Thiongane, A., Ndiaye, O., Luwanda, L. B., . . . **Tan, Rainer** (2023). [Paediatric digital clinical decision support for global health]. *Rev Med Suisse, 19*(836), 1398-1403. doi:10.53738/revmed.2023.19.836.1398
- **Tan, Rainer**., Cobuccio, L., Beynon, F., . . . D'Acremont, V. (2023). ePOCT+ and the medAL-suite: Development of an electronic clinical decision support algorithm and digital platform for pediatric outpatients in low- and middle-income countries. *PLOS Digital Health, 2*(1), e0000170. doi:10.1371/journal.pdig.0000170
- Trottet, C., Vogels, T., Keitel, K., Kulinkina, A. V., **Tan, Rainer,** Cobuccio, L., . . . Hartley, M. A. (2023). Modular Clinical Decision Support Networks (MoDN)-Updatable, interpretable, and portable predictions for evolving clinical environments. *PLOS Digit Health, 2*(7), e0000108. doi:10.1371/journal.pdig.0000108

- **Tan, Rainer**, Emery, N., Miauton, A., Genton, B., & D'Acremont, V. (2022). [Eco-tourism: what recommendations?]. *Rev Med Suisse, 18*(780), 886-889. doi:10.53738/revmed.2022.18.780.886
- Chandna, A.*, **Tan, Rainer***, Carter, M., Van Den Bruel,. . . Keitel, K. (2021). Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies. *BMJ Glob Health, 6*(1). doi:10.1136/bmjgh-2020-003451 ***Co-primary author**
- van de Maat, J., De Santis, O., Luwanda, L., **Tan, Rainer**, & Keitel, K. (2021). Primary Care Case Management of Febrile Children: Insights From the ePOCT Routine Care Cohort in Dar es Salaam, Tanzania. *Front Pediatr, 9*(465). doi:10.3389/fped.2021.626386
- **Tan, Rainer**, Kagoro, F., Levine, G. A., . . . Keitel, K. (2020). Clinical Outcome of Febrile Tanzanian Children with Severe Malnutrition Using Anthropometry in Comparison to Clinical Signs. *American Journal of Tropical Medicine and Hygiene, 102*(2), 427-435. doi:10.4269/ajtmh.19-0553
- Miauton, A.*, **Tan, Rainer***., Pantazou, V., Du Pasquier, R., & Genton, B. (2020). Vaccine-associated measles in a patient treated with natalizumab: a case report. *BMC Infectious Diseases, 20*(1), 753. doi:10.1186/s12879-020-05475-9 ***Co-primary author**
- **Tan, Rainer**, Elmers, J., & Genton, B. (2019). Malaria standby emergency treatment (SBET) for travellers visiting malaria endemic areas: a systematic review and meta-analysis. *J Travel Med, 26*(4). doi:10.1093/jtm/taz027
- **Tan, Rainer**, Hugli, O., Cavassini, M., & Darling, K. (2018). Non-targeted HIV testing in the emergency department: not just how but where. *Expert Rev Anti Infect Ther, 16*(12), 893-905. doi:10.1080/14787210.2018.1545575