Manuscript Research article

BMC Medical Informatics and Decision Making

TITLE

Connected Diagnostics to improve accurate diagnosis, treatment, and conditional payment of malaria services in Kenya.

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Wordcount manuscript: 4739

Excluding abstract, declarations and description of figures

ABSTRACT

Background: In sub-Saharan Africa, the material and human capacity to diagnose patients reporting with fever to healthcare providers is largely insufficient. Febrile patients are typically treated presumptively with antimalarials and/or antibiotics. Such over-prescription can lead to drug resistance and involves unnecessary costs to the health system. International funding for malaria is decreasing and transition to domestic funding is challenged by UHC efforts and recent COVID-19 outbreak. Herewith we present a digital approach to markedly improve efficiencies in diagnosis and treatment of malaria in endemic Kisumu, Kenya. The objective of this study is to evaluate feasibility, user experience, clinical performance and of Connected Diagnostics in Kisumu and to assess over-prescription of antimalarials.

Methods: Our intervention was performed Oct 2017 – Dec 2018 across seven providers in Kisumu. Patients were enrolled on M-TIBA platform, diagnostic test results digitized, and only positive patients were digitally entitled for malaria treatment. Data on socio-demographics, healthcare transactions and medical outcomes were analysed using standard descriptive quantitative statistics. Provider perspectives were gathered by 19 semi-structured interviews.

Results: In total 11,689 febrile patients were tested. Malaria positivity rates ranged from 7.4% to 30.2% between providers, with significantly more positive cases amongst the poor ($p < 0.05$). Over-prescription of antimalarials was 28%, fluctuating between 4.6% to 63.3% per provider. Prescription of branded versus generic antimalarials was dichotomous. Challenges were encountered transitioning from microscopy to RDT.

Conclusion: We provide full proof-of-concept of innovative Connected Diagnostics to use digitized malaria diagnostics to earmark digital entitlements for correct malaria treatment of patients. This approach has large cost-saving and quality improving potential.

Keywords: Diagnosis, Treatment, Conditional payments, Malaria, Kenya, Connected Diagnostics

MANUSCRIPT

Background

Sub-Saharan Africa (SSA) continues to face challenges attaining accurate diagnosis of both infectious and non-communicable illnesses. Laboratory diagnosis remains suboptimal with much-needed lab equipment often lacking, financial resources being scarce and skilled medical staff underrepresented [1]. Recently across 49 SSA countries only 380 laboratories were found to be accredited against international standards, with many countries not even hosting one single accredited provider [2]. Also in urban and semi-urban centers where lab facilities and staff are usually better available, inaccurate diagnoses with limited sensitivity and specificity are common practice [1, 3-5]. Fever is one of the most common reasons people in Africa visit health providers. However, due to the aforementioned challenges with lab providers across the continent, febrile patients are often not diagnosed using laboratory tests, but only presumptively, based on clinical grounds [1]. The most common presumptive diagnosis in febrile patients is malaria, followed by bacterial infection(s), resulting in over-prescription of antimalarials and antibiotics. A recent study indicated that more than 70% of fever cases in Tanzanian children was caused by viral infections, against which antimalarials and antibiotics do not work [6].

SSA countries hold a disproportionately high share of global malaria burden. In 2018, the region hosted 93% of malaria cases and 94% of malaria deaths [7]. Over 99% of malaria cases in malaria endemic areas of Africa were caused by *P. falciparum* in 2018 [7]. The malaria morbidity and mortality in Africa cost the continent more than 12 billion USD annually in GDP [8, 9]. Furthermore, global funding for malaria control and elimination in Africa is flat-lining and the recent call for universal health coverage (UHC) puts pressure

on traditional vertical funds for malaria, such as the Global Fund to Fight Aids Tuberculosis and Malaria (GFATM) and President's Malaria Initiative (PMI) [10, 11]. Additional challenges to malaria service delivery are emerging with the recent outbreak of COVID-19 [12]. Important drawbacks in combatting malaria were encountered in West Africa during the recent Ebola outbreak, setting examples for responding to the imminent COVID-19 pandemic [13], indicating importance of more efficient, targeted digital malaria service delivery.

Because of presumptive diagnosis and treatment for malaria in febrile patients, over-prescription of malaria drugs in malaria endemic African countries is common [14, 15]. This can have key health implications, including development of drug resistance, higher risk of treatment failure, increased morbidity. In addition, it leads to economic implications such as unnecessary drug costs, recurring visits, and economic productivity losses due to longer sick days. Due to this, the costs for both households and healthcare providers increases [16, 17]. Moreover, prescription of drugs that are ineffective can lead to reduced patient trust in healthcare provision with subsequent decreased willingness to participate in financial (insurance) schemes for pre-payment and risk-sharing.

Recent developments in the area of digital technology provide new opportunities to address the above situation in a radically different way. Firstly, the emergence of the Internet of Things (IoT) comprising a rapidly growing arsenal of 'digital diagnostics': tools and devices that digitalize and link human physical parameters to the internet, complete with sensing and measuring capabilities [18]. Secondly, the mobile revolution: 75% of the African population has access to a mobile phone. In Kenya, mobile penetration is at 86%, and still growing rapidly [19, 20]. Thirdly, Africa is leapfrogging with the advent of 'bankless banking': digital payment systems through mobile phones transferring entitlements between individuals. An example of this is M-PESA, launched in 2007 in Kenya: an electronic mobile money service to store, send and receive money on any mobile phone (smartphone or non-feature) with an M-PESA account [21].

Since 2014 the non-profit foundation PharmAccess has leveraged these developments to create a 'mobile health wallet' linked to the M-PESA payment platform, known as M-TIBA ('mobile therapy' in Swahili). Today, M-TIBA is hosted by CarePay International and represents the first African digital platform exchanging data and funds/entitlements that are exclusively earmarked for health and healthcare [22]. M-TIBA works on simple, non-feature mobile phones as well as smartphones. It connects patients, healthcare providers and healthcare payers (such as insurers and donors) and exchanges data and entitlements between them. Users can save into their own (family) wallets, they can receive money from relatives elsewhere in the country, from donors, and even from individuals in other countries willing to donate directly for health [23]. This is a first step in creating new digital solidarity mechanisms where people can financially contribute to each other's health: the rich for the poor, the healthy for the sick, the young for the old, and communities for individuals. As of April 2020, 4.2 million people in Kenya, Nigeria, Tanzania and 1,500 health providers on the continent were connected to the platform [22].

Given above developments, we saw an opportunity within the Kenyan context to combine digital diagnostics and M-TIBA technology to support marked improvements in the efficiency of diagnosis and treatment of febrile diseases. This approach is referred to as 'Connected Diagnostics (ConnDx)'. ConnDx introduces a new system-wide digital delivery approach for malaria care, linking phones to diagnostics and payment systems. Providing ConnDx services, yields simultaneous real-time insight into data and funds exchanged between patients, providers, and healthcare payers.

ConnDx digitalizes rapid diagnostic tests (RDTs) through photography and interprets and stores results in cloud-based databases through dedicated RDT readers. Such readers are available, like the Fio Deki Reader™[1], i-CalQ lateral flow-test imaging[2] and the Mobile Assay 'lab-on-mobile device' platform[3]. The

[1] http://fio.com/rapid-testing/
[2] https://i-calq.com/technology/
[3] https://mobileassay.com/

digital diagnostic results subsequently inform a mobile phone-based payment system (M-TIBA) to channel dedicated funds for diagnosis and treatment of the pertinent disease to the provider and/or patient. A recent proof-of-principle of ConnDx, was provided in Samburu, Kenya, in which RDTs interpreted by the Fio Deki Reader™ were used to diagnose brucellosis in remote populations [24]. Brucellosis, a rare bacterial zoonotic illness, is often underdiagnosed due to having similar febrile symptoms as malaria [25]. Patients testing positive were directly linked to funds through their respective mobile health wallets to allow for payment of drugs for the pertinent diseases, conditional to positive diagnosis of these diseases. Feasibility was demonstrated, patients were correctly treated, their user experience was positive, and hotspots of brucellosis were identified [24].

Having proven that ConnDx could be effective in identifying a rare disease in rural, remote populations, this paper reports on the next step: scaling ConnDx to a more densely populated area for a more prevalent disease (malaria) that causes high morbidity, mortality and serious economic impact. The objective of this study is to evaluate feasibility, user experience, and clinical performance of a ConnDx intervention in Kisumu, Kenya. Additionally, the aim is to assess over-prescription of antimalarials in this population. The location of choice, Kisumu County in Kenya, has a population of 1.2 million [26], and a reported high malaria prevalence of approximately 28-35% in the general population [27, 28]. Our intervention took place from October 2017 – December 2018 amongst seven private sector health providers and ~12,000 beneficiaries.

Methods

The ConnDx process starts upon patient presentation at participating providers or healthcare outreach events. The project was announced to the public through posters in the waiting room referring to a free 'Malaria Test & Treat Campaign'. Consenting patients presenting with fever and/or malaria symptoms were

143 referred by informed clinicians for malaria testing by qualified lab technicians using malaria RDTs,
144 digitalized using a Fio Deki Reader^{TM}. The Reader contained a drop-down menu to collect demographic
145 data (gender, age, pregnancy status), basic economic data (socio-economic status) and geographic location
146 data (community of residence, to a granularity level of 3,000-5,000 citizens). For socio-economic status
147 assessment three questions were added to the menu pertinent to access to electricity, toilet type and
148 education level of household head. These questions had been previously identified most informative by
149 principal component analysis using a Multiple Indicator Cluster Survey in Nyanza for reference [29]. This
150 led to a poverty index, in which level 1 corresponds to the poorest category; level 3 to the least poor.
151
152 Simultaneously, the participating patients were enrolled on the M-TIBA platform and individual health
153 wallets were created. The collected Fio Deki Reader^{TM} demographic data, along with patient test results,
154 was uploaded to the Fionet cloud database and linked to the patient's mobile health wallet account using a
155 unique M-TIBA transaction code. Only patients with a positive diagnosis were entitled to receive funding
156 for antimalarials, which (in an interim functionality) was paid to their respective healthcare providers, thus
157 effectuating fully paid treatment for the patients. Figure 1 provides a schematic illustration of the ConnDx
158 process.
159
160 ConnDx was implemented from October 2017 – December 2018 across seven private care providers
161 (anonymized A-G) within sub-counties of Kisumu County. The providers were a part of an existing care
162 system. They were selected based on (high) patient throughput and geographic location and ranged from
163 smaller providers with set opening hours to large 24/7 hospital facilities. The National District Health
164 Information System (DHIS-2) software was used as data source for selection of providers.
165
166 The provider perspectives on the use of ConnDx were gathered by means of 19 semi-structured interviews
167 in the seven participating health providers. Interviewed staff were managers, lab technicians, receptionists,

and doctors or nurses. The interviews were analyzed by applying a thematic analysis approach using the software Atlas.ti to identify patterns or topics within the data.

Quantitative data from both cloud-based databases (FIO and M-TIBA) were analyzed through descriptive statistics in Stata 12 and Microsoft Excel 2016. Descriptive analyses were done for each provider separate and over time. Relationships between categorical variables were tested by using the chi-square test to calculate p-values and compare proportions between groups. A p-value of <0.05 was considered statistically significant. For geographic location analyses, the subdivision of Kisumu County was divided into the 163 administrative community units, each with roughly 1,000-1,200 households. Participants were asked at point of care which community unit their home was based. Geographic analyses were performed in QGIS (Version 3.0) by using the geographic center of each community unit as a proxy for the location of the participants' domicile. The project was positioned as a quality improvement project of existing malaria services according to Kenyan Guidelines. It was run in parallel to existing systems and services. All study participants provided consent for participation prior to the enrolment process into M-TIBA. Verbal informed consent was obtained from provider interviewees prior to the interview.

Results

Between October 2017 and December 2018, 11,689 people with fever were tested in 7 private providers (A-G). Figure 2 depicts the numbers of malaria RDTs uploaded by location of these providers and participants' domiciles according to the community unit they reported to live in.

Figure 3 shows the participation dynamics per provider during the intervention. Providers A and B discontinued participation after 5 months; providers E, F and G enrolled in April 2018 and continued until the end of the project. Providers A and B are not included in further analyses, due to the insufficient amount of data for the study period. Malaria testing rates coincided with the rainy seasons in Kisumu for 2017 and

2018 (“long rains” from March to June, and “short rains” from October to December), known to increase malaria transmission. During the study period (2018), rainfall in Kisumu was particularly high and prolonged compared to the average [30].

Variation between the providers was found regarding positivity rates of malaria tests. Provider D reported relatively the least positive malaria tests (7.4%; 290/3,908). This is followed by provider E (12.6%; 127/1,006), provider G (16.7%; 279/1,666) and provider C (18.1%; 460/2,548). Provider F identified the highest percentage of positive malaria cases (30.2%; 922/3,057).

From all 11,689 consenting patients who were tested for malaria, there was an 18.3% overall test positivity rate. Although more women were tested (58.2%), more male positive cases (19.0%; 993/7,297) were found (15.4%; 1,126/7,297). The mean age of patients was 23.6 years and 16.5% of patients were aged under 5 years old. For children under 5 years of age, the percentage of positive malaria cases was comparable to adults 17.7% (n = 340/1,926). From the participants, 63.1% were member of NHIF, the national health insurance in Kenya. Patients in poverty level 1 were significantly more often tested positive for malaria than patients with a higher poverty score (*p-value < 0.05*).

The RDT results uploads of ConnDx allowed for quality assessment, since the Deki Reader™ indicates ‘error’ at point of care when the RDT is not performed correctly. Figures 4a-c illustrate quality improvement of RDT performance represented by reductions of error rates over time. Figure 4a demonstrates considerable overall improvement over the first month of RDT usage (from 25% range down to below 5%). Figures 4b and 4c provide individual data for later starters G (improvement) and F (continued good performance).

For all participating providers, general over-prescription of antimalarials was observed. Over-prescription is defined by the proportion of antimalarials dispensed to the actual number of positive cases as identified

by a positive malaria test. The overall over-prescription was 28.0%, fluctuating between 4.6% (provider F) and 63.3% (provider D). There were fluctuations in over-prescription over time, as illustrated in Figure 5. High over-prescription rates were recorded prior to the introduction of ConnDx at provider D. During the ConnDx intervention over-prescription declined significantly. Only towards the end of the intervention, an increase was observed.

Figure 6 demonstrates M-TIBA derived information on individual provider specific prescribing behavior in choices of drugs (1st line and 2nd line) for antimalarials. The most common prescriptions were: artemether/lumefantrine (75.4%, either branded (Coartem, 43.7%) or generic (28.5%), followed by artemether injection, a 2nd line drug (15%). Overall, 75.6% of all antimalarials dispensed by the providers were 1st line and 24.4% were 2nd line. It was found that 2nd line antimalarials were significantly more frequently prescribed to the more affluent population and to participants who were not insured with NHIF (p-value <0.05). Provider C dispensed most 2nd line antimalarials (average 53.7, ranging from 26.5% - 100.0%). This is followed by provider F (24.7%), provider D (9.2%), provider G (7.1%) and provider E (3.9%). Figure 6 illustrates that three (C, E, F) out of five private providers significantly diverted from the Kenyan guidelines for prescription. The choice of branded versus generic antimalarials appeared dichotomous: providers C, D and G prescribed predominantly generics and providers E and F branded drugs.

Our qualitative interviews with healthcare providers identified several opportunities and challenges of ConnDx. In general, positive feedbacks were received by all interviewees. Malaria diagnosis through RDT was experienced by 14 of 19 providers as easier, more efficient, and faster. Interviewed providers (14/19) predominantly mentioned patients were also positive towards this way of testing for malaria and receiving payments for treatment. In addition, healthcare providers predominantly (13/19) appreciated ConnDx providing interesting additional (management) information on patients, prescription practices and drug procurement. Interviewees (16/19) indicated ConnDx to be an effective means to expand access to malaria

treatment for the poor and for children. Overall, 13 of 19 providers reported an increased awareness that diagnostics should determine treatment decisions, and thereby reduce the prescriptions of unnecessary drugs. One of the challenges most frequently mentioned by healthcare providers (14/19) was a persistent lack of trust in RDTs.

Discussion

This study describes feasibility, user experience and clinical performance through healthcare providers in Kisumu of a novel digital approach to malaria diagnosis that directs conditional payments for malaria treatment: ConnDx. We demonstrate significant potential for increasing efficiencies of malaria service delivery in the Kenyan private healthcare sector with respect to better diagnosis, reducing over-prescription, selecting correct 1st and 2nd line drug combinations and reducing malaria transaction costs, while at the same time generating valuable real-time data on malaria prevalence and incidence (hotspots) that can be fed into national information systems (such as DHIS-2).

First of all, ConnDx proved through this pilot its potency to monitoring malaria epidemiology in semi-real time and generate important data for malaria management. Considerable variation was revealed between providers, with malaria positivity rates ranging from 7.4% (provider D) to 30.2% (provider F). This led to verifiable assumptions such as Provider D being a referral hospital and therefore less likely to serve primary malaria cases, while provider F, being located near wet rice fields, serving known hotspots for malaria. During months with more rainfall, there were significantly more malaria tests done at the providers (p-value <0.05). However, no significant correlation was found between months with more rainfall and positive malaria test results. Providers located in or near low-income settlements (C and G) appeared to have higher malaria positivity rates, as a correlation between poorer patients and positive malaria tests was found (p-value <0.05). ConnDx showed a relatively low participation rate of children: only 16.5% of reported patients were aged <5 years. Moreover, positive malaria rates in this age group were not different from

adults: 17.7%. This seems an underestimation of the cases, as children under five are at considerably higher risk of contracting malaria than adults. They are also the most vulnerable group affected by malaria, WHO estimated 67% of malaria deaths globally were children <5 years old in 2018 [7]. Our qualitative interviews with providers revealed that clients experienced challenges subscribing their children to M-TIBA as dependents, therefore erroneously reporting them as adult primary members. This was corrected later during the campaign but could have contributed to general underreporting of pediatric malaria cases. All in all, it was clearly demonstrated that ConnDx can facilitate in semi-real time important healthcare provider-differences in malaria case management. Such information, when collected at a larger-scale level could help policy makers and health system managers to target their efforts for (human) malaria capacity building.

Secondly, this study demonstrated the overall potency of ConnDx to monitor provider prescription behaviors and identify practices that are significantly aberrant from Kenyan National Guidelines. Important overall over-prescription was recorded of antimalarials (28.0%), varying between providers from 4.6% (provider F) to 63.3% (provider D). There are multiple reasons for over-prescription, ranging from monetary considerations of private providers, to patient expectation and pressure to receive drugs, avoidance of clinicians to take the risk of a false negative diagnosis and subsequent fatality, etc. [15]. Our qualitative interviews mostly pointed towards patient pressure (10/19 interviewees). Furthermore, ConnDx revealed an unexpected and erroneously high level of prescription of 2nd line antimalarials (overall 28.0%). Provider C revealed 2nd line prescription levels of overall 53.7%, at times going up to even 100%. This is remarkable, as 2nd line antimalarials are generally used for severe cases of malaria, which represent on average <2% [31], or in (rare) cases of suboptimal parasitological response with 1st line antimalarials (resistance). When probed with this observation, provider C reported a prolonged stock-out of 1st line antimalarials and therefore switching to 2nd line. Over-prescription of 2nd line antimalarials was significantly more frequently found with more affluent and uninsured participants. This could indicate providers are aware of the socio-economic status of their clients and they incorporate this into their prescriptions. Moreover, it appeared there was a very dichotomous, almost exclusive usage of either branded (provider E

294 and F) or generic (provider C, D, G) antimalarials. This could be because providers serving more affluent
295 customers prefer procurement of branded versus generic antimalarials. Conversely, more affluent
296 customers might request for branded instead of generic antimalarials. Often, generic medicines are
297 considered to be of poor quality and treated with more suspicion than branded medicines [32, 33].
298
299 Third this study indicates that ConnDx can increase efficiency in malaria service delivery by decreasing
300 costs in several ways. Over-prescription of antimalarials can be monitored, aberrations identified, and
301 actions undertaken to address those. A 2013 study conducted in four providers in western Kenya, noted that
302 presumptive malaria treatment lead to misdiagnosis rates as high as 53%. The same study found that as
303 many as 36% of patients diagnosed with malaria via microscopy should be classified as false positives [14].
304 ConnDx can play an important role to reduce such figure. Further cost reductions can potentially be realized
305 by ConnDx decreasing paperwork in health providers; such automated systems saving time, manpower and
306 being more accurate in reporting cases [34]. In addition, ConnDx implies less dependency on expensive
307 and maintenance-dependent microscopy, and less electricity will be required to perform diagnostics tests.
308 Moreover, due to its use-friendliness ConnDx, will provide more opportunities for lower trained lab-staff
309 to perform such tests, saving personnel costs. Finally, and most importantly, ConnDx can facilitate a much
310 more targeted bottom-up payment for malaria services to providers and clients, creating unprecedented
311 transparency as compared to current top-down systems.
312
313 Overall user experiences of ConnDx from the perspectives of providers were positive. Nevertheless, after
314 five months of implementation, in February 2018 two providers, A and B, dropped out of the pilot. Probed
315 through our interviews, these providers reported reluctance of their patients (who were already covered by
316 NHIF) to go through the administrative process of registering with M-TIBA. Other, more general
317 challenges identified were technical, such as dependency of ConnDx from internet connectivity. However,
318 for all providers, the key challenge were reservations of their staff to adopt the use of RDTs instead of
319 microscopy. In general, microscopy was still seen as the golden standard for malaria testing in Kenya,

despite National Guidelines indicating equality of RDT and microscopy as diagnostic procedure [35]. Some healthcare providers mentioned they verified RDT results by microscope.

Indeed, ConnDx is dependent on the use of RDTs instead of microscopy for malaria diagnostic testing. Apart from National Guidelines, also the international literature reports sensitivity and specificity of malaria RDTs equal to microscopy [36, 37]. RDTs are also recommended by WHO [3]. Several studies demonstrated impaired sensitivity of microscopy in actual field situations in Africa as compared to perfectly controlled laboratory circumstances, with regular refresher training being required [33, 34]. RDTs have the added advantage that, in contrast to microscopy, these can easily be externally quality controlled by visual inspection of independent third parties. This opportunity is further enhanced through the ConnDx feature of making digital photographs of every test result, stored in secure cloud-based databases that can be accessed anywhere in the world. Additional advantage of RDT is that results can be digitalized, which accelerates data collection to (semi)real-timeliness, allows for telemedicine-based quality control and improves quality and completeness of data collection (versus paper-based malaria files being entered into national DHIS-2 systems on a several-time-per-year basis). These options are all much more problematic when performing microscopy. Moreover, in the sub-Saharan African reality, RDTs can readily detect *Plasmodium falciparum*, which causes the highest malaria morbidity and mortality and represents 99.7% of cases [35]. RDTs indeed are less available that specifically detect *P. vivax*, but this species is virtually absent in the region. Finally, indeed RDTs can provide a false-positive result with patients who had recent malaria episodes. This can be addressed by building a feature into the ConnDx algorithm that patients should be asked whether (s)he experienced malaria episodes in the past 1-2 months and if so, microscopy should be prioritized.

All in all, the clinical and economic impact of using RDTs for diagnosing febrile diseases, such as malaria, deserves further attention and studies indicate that this largely depends on the actions undertaken following RDT results. A recent review demonstrated 45% of patients testing negative for malaria with RDTs still

346 being prescribed antimalarials by community health workers [38, 39]. The above outlined challenges
347 suggest diagnostics tests for febrile diseases, such as RDTs, should be embedded in a digital infrastructure
348 of logistics and human decision support to raise to the next level of effectiveness and cost reductions. In
349 the future, ConnDx could be deployed for bacterial infections as long as these can be diagnosed by RDTs,
350 leading to better-informed antibiotic prescriptions. This is important in fighting antimicrobial resistance
351 [40].
352
353 This study has several strengths and weaknesses. Strength is the important innovation of ConnDx providing
354 reliable, geo-tagged and semi-real-time insights in malaria diagnostic and therapeutic services by private
355 sector providers in a semi-rural setting in Kenya. Kisumu county hosts 94 private providers, which deliver
356 approximately half of all primary healthcare services to its population (the government supplying care
357 through 148 additional providers). With the far majority (1 million) of Kisumu citizens currently connected
358 to M-TIBA [41], ConnDx could in principle rapidly be scaled to all private providers and supplement the
359 governments' DHIS-2 database with valuable real-time private sector information. Another strength is the
360 pioneering nature of this study that was supported by the local health authorities to run in parallel to existing
361 malaria services. This allowed for rapid collection of important data, leading to actionable information for
362 policy makers who demonstrated strong involvement.
363
364 In terms of weaknesses, this study was an observational study and not a formal clinical trial. Therefore,
365 there are no statistically validated results on (improved) diagnostic performance and (improved) clinical
366 outcomes with respect to malaria. Moreover, in this study there were no special provisions taken for febrile
367 patients who were testing negative for malaria and pertinent consequences with respect to changes in
368 clinical decision making. For example, it was not studied what the effect was of reduced malaria
369 prescription on provider prescription of alternative drugs for fever (in particular, antibiotics) and what were
370 the clinical consequences of such decisions. Furthermore, as the ConnDx process was not yet fully
371 digitalized, several steps were still performed manually, such as linkage of cloud-databases and payout

mechanisms. Therefore, the study did not allow for direct and automated feedback-loops with any of the participating stakeholders (patients, providers, payers, policy makers). For this reason, progress observed with respect to quality improvement or increased cost-efficiency during this pilot, was modest and likely mostly due to the realization of providers that they were being remotely observed by the ConnDx intervention. There were also external factors that influenced the ConnDx pilot, such as civil unrest due to national elections, which hindered uptake of participants due to security issues. There were several strikes of medical staff that put constraints on general malaria service provision. Moreover, M-TIBA is using Safaricom as mobile operator (with a market share of 70% of Kenya), which became political in Kisumu where most of the population is from other tribal background than the Safaricom ownership, resulting in temporary boycotts of usage of this platform. Finally, it should be kept in mind that ConnDx was implemented in parallel to existing malaria services covered by the NHIF and the MoH. Thus, health providers could in principle benefit by participating in two parallel financing mechanisms, which could potentially create perverse incentives. This would obviously not be the situation when ConnDx is fully integrated into NHIF or any other UHC prepayment mechanism and made a compulsory condition for payouts.

Conclusions

This paper demonstrates the potential of ConnDx for more efficient malaria services at scale. ConnDx links important datasets in (semi) real-time, which previously were in silos and reported irregularly in DHIS-2. This allows for improved efficiencies at all levels of the healthcare system. For clients, the quality of care can improve by avoiding over-prescription of ineffective drugs and by providing the possibility to save and remunerate funds for malaria. Moreover, the linkage of patients' telephone numbers to the platform allows for additional services like malaria information, appointment keeping, adherence support, patient feedback loops to providers on experienced quality of care, individual alarms, early warning systems for geographic malaria hotspots, etc. For providers, better information is given with respect to its diagnosis and treatment

performance versus the National Guidelines, benchmarked and rated against colleagues. Moreover, providers save capitation fees when ConnDx is integrated into NHIF services, avoiding over-prescription of antimalarials. Finally, reputation will be increased due to better-quality care delivered. For payers, ConnDx reduces overhead costs by increasing transparency, supporting healthcare transactions at marginal costs. Funding can be traced to pertinent individual patient cases and vertical malaria funds can be integrated into larger UHC funding pools, covering both public and private sector. For Kenyan policy makers and healthcare managers, ConnDx opens ample opportunities to timely identify weaknesses in service delivery and undertake targeted remedial actions, such as specific training to providers.

With ConnDx linking cloud-based databases of digital diagnostics data to a digital healthcare exchange platform such as M-TIBA, diagnostic results can target entitlements for malaria treatment directly through the mobile phones of M-TIBA users. This improved financial transparency, combined with marked quality gains through ConnDx presents a valuable proposition for scaling through (inter)national funders, such as the NHIF in Kenya, supported by the GFATM to channel vertical malaria funds through M-TIBA-facilitated payment platforms and contribute to UHC. ConnDx offers ample opportunities to enable more efficient service delivery for other high-morbidity medical conditions that can be digitally diagnosed, such as cervical cancer and cataract.

Abbreviations

ConnDx: Connected Diagnostics; DHIS-2: District Health Information Software; GFATM: Global Fund to Fight AIDS, Tuberculosis and Malaria; IoT: Internet of Things; MoH: Ministry of Health; NHIF: National Hospital Insurance Fund; PMI: President's Malaria Initiative; SSA: sub-Saharan Africa; UHC: Universal Health Coverage; WHO: World Health Organization

Declarations

Ethics approval and consent to participate

Written permission was obtained from the Kisumu Department of Health to conduct this study. This paper describes an operational project that was rolled out in Kisumu, Kenya in full coordination with the local Department of Health. The project was not positioned as a research study and therefore no formal ethical clearance was applied for. Rather, we performed this work as an implementation project to improve efficiency of malaria service delivery through innovative digital approaches. As such, this project was approved by the County Chief Office of Health, Dr Dickens Oyango.

The Participants of this program were verbally informed about the program by their clinician. When choosing to participate in this program, they subscribed to the M-TIBA digital mobile health platform, which asks clients a question of consent when first registering. For the interviews, verbal and written consent was obtained from the respondents. Confidentiality of research subjects and personnel records was ensured by anonymizing data collection. No individual participant data is disclosed within this manuscript in any form.

Consent for publication

Not applicable.

Availability of data and materials

Due to privacy of patient data, datasets associated with this project are not publicly available. Anonymized data is available from the authors upon request.

Competing interests

The authors declare no conflicts of interest

Funding

This study was supported by seed funding from the Joep Lange Institute as well as funding from the Ministry of Foreign Affairs of the Netherlands. The funders of this work had no role further in the study. Their funds were solely used for the implementation of Connected Diagnostics as a digital innovation as part of PharmAccess operations in Kenya.

Authors' contributions

TRW designed the concept, the implementation research study and scientifically supervised the project. EM, AS and EO were responsible for onsite day-to-day operations during the intervention and contributed substantially to data acquisition. MO and MA supported facilitation of the project in health facilities in Kisumu and contributed to collection of data. SD, TRW, LS and SS analyzed and interpreted the data and wrote the first draft manuscript. LS provided complementary essential statistical support. TK provided malaria-specific information for Kisumu, technical assistance to the project and critical review of the paper. DO and LD represented the Kisumu Department of Health, provided policy support, facilitated operations,

reviewed the paper and provided complementary contextual information regarding healthcare access and details on malaria healthcare provision in Kisumu. All authors contributed to writing of this manuscript and have approved the final version of the manuscript for submission.

Acknowledgements

The authors would like to express gratitude to all clinicians, nurses, lab technicians, and M-TIBA agents who were involved in the field work of this study, and the respondents who participated in the interviews. We would also like to thank the Kisumu Department of Health for its permission and cooperation to execute this study. Seed funding for this project was generously provided by the Joep Lange Institute.

References

1. D'Acremont, V., et al., *Time to move from presumptive malaria treatment to laboratory-confirmed diagnosis and treatment in African children with fever.* PLoS Med, 2009. **6**(1): p. e252.
2. Schroeder, L.F. and T. Amukele, *Medical laboratories in sub-Saharan Africa that meet international quality standards.* Am J Clin Pathol, 2014. **141**(6): p. 791-5.
3. Organization, W.H., *A report on the misdiagnosis of HIV status*. 2014, World Health Organization. p. 31 p.
4. WHO, *Guidelines for the Treatment of Malaria - 2nd Edition*. 2010, World Health Organization. p. 210 p. .
5. Yegorov, S., et al., *Low prevalence of laboratory-confirmed malaria in clinically diagnosed adult women from the Wakiso district of Uganda.* Malar J, 2016. **15**(1): p. 555.
6. D'Acremont, V., et al., *Beyond malaria--causes of fever in outpatient Tanzanian children.* N Engl J Med, 2014. **370**(9): p. 809-17.
7. WHO, *World Malaria Report 2019* 2019, World Health Organization: Geneva.
8. Cibulskis, R.E., et al., *Malaria: Global progress 2000 - 2015 and future challenges.* Infect Dis Poverty, 2016. **5**(1): p. 61.
9. Patouillard, E., et al., *Global investment targets for malaria control and elimination between 2016 and 2030.* BMJ Glob Health, 2017. **2**(2): p. e000176.
10. *President's Malaria Initiative (PMI)*. 2019 31 December 2019]; Available from: https://www.pmi.gov/.
11. *The Global Fund*. 2019 31 December 2019]; Available from: https://www.theglobalfund.org/en/.
12. Wang, J., et al., *Preparedness is essential for malaria-endemic regions during the COVID-19 pandemic.* The Lancet 2020.
13. Jones, S.A., et al., *'Women and babies are dying but not of Ebola': the effect of the Ebola virus epidemic on the availability, uptake and outcomes of maternal and newborn health services in Sierra Leone.* BMJ Glob Health, 2016. **1**(3): p. e000065.
14. Afrane, Y.A., et al., *Utility of health facility-based malaria data for malaria surveillance.* PLoS One, 2013. **8**(2): p. e54305.
15. Oladosu, O.O. and W.A. Oyibo, *Overdiagnosis and Overtreatment of Malaria in Children That Presented with Fever in Lagos, Nigeria.* ISRN Infectious Diseases, 2013.
16. Hume, J.C., et al., *Household cost of malaria overdiagnosis in rural Mozambique.* Malar J, 2008. **7**: p. 33.

17. Were, V., et al., *Socioeconomic health inequality in malaria indicators in rural western Kenya: evidence from a household malaria survey on burden and care-seeking behaviour.* Malar J, 2018. **17**(1): p. 166.
18. Miorandi, D., S.D.P. Sicari, F., and C. I., *Internet of things: Vision, applications and research challenges.* Ad Hoc Networks, 2012. **10**: p. 1497–1516.
19. Chutel, L. *Africa's largest phone network is expanding its dominance with its own "smart feature phone"* 2018 31 December 2019]; Available from: https://qz.com/africa/1464244/africas-largest-phone-network-is-expanding-its-dominance-with-its-own-smart-feature-phone/.
20. Databank, W. *World Development Indicators - Mobile Cellular Subscriptions 2017* 2017 31 December 2019]; Available from: https://databank.worldbank.org/data/source/world-development-indicators.
21. Safaricom. *Safaricom - MPESA*. 2019 31 December 2019]; Available from: https://www.safaricom.co.ke/personal/m-pesa.
22. *M-TIBA Dashboard*. 2019 31 December 2019]; Available from: http://pharmaccess.m-tiba.org/home.
23. Foundation, P. *HealthConnect.* 31 December 2019]; Available from: https://www.healthconnectme.org/.
24. Smith, S., et al., *Connected diagnostics: linking digital rapid diagnostic tests and mobile health wallets to diagnose and treat brucellosis in Samburu, Kenya.* BMC Med Inform Decis Mak, 2019. **19**(1): p. 139.
25. Abdelhady R, A.K., Elhussein A., *Prevelance of brucellosis among febrile negative malaria patients by PCR in Northern Kordofan State, Sudan.* . Clin Microbiol, 2017. **6**(293): p. 2.
26. KNBS, *2019 Kenya Population and Housing Census Volume I: Population by County and Sub-County*. 2019, Kenya National Bureau of Statistics.
27. Jenkins, R., et al., *Prevalence of malaria parasites in adults and its determinants in malaria endemic area of Kisumu County, Kenya.* Malar J, 2015. **14**: p. 263.
28. *Kisumu County - Health at a glance*. 2015 31 December 2019]; Available from: https://www.healthpolicyproject.com/pubs/291/Kisumu%20County-FINAL.pdf.
29. WorldBank. 31 December 2019]; Available from: https://microdata.worldbank.org/index.php/catalog/2660.
30. *Kisumu Monthly Climate Averages - Rainfall and Rain Days* [cited 2020 February, 6]; Available from: https://www.worldweatheronline.com/kisumu-weather-averages/nyanza/ke.aspx.
31. *Kenya Malaria Indicator Survey 2015* 2016, ICF international, Kenya National Bureau of Statistics Nairobi, Maryland

32. Patel, A., et al., *Quality of generic medicines in South Africa: perceptions versus reality - a qualitative study.* BMC Health Serv Res, 2012. **12**: p. 297.
33. Fadare, J.O., et al., *The prescribing of generic medicines in Nigeria: knowledge, perceptions and attitudes of physicians.* Expert Rev Pharmacoecon Outcomes Res, 2016. **16**(5): p. 639-650.
34. Kalogriopoulos, N.A., et al., *Electronic medical record systems for developing countries: review.* Conf Proc IEEE Eng Med Biol Soc, 2009. **2009**: p. 1730-3.
35. Ministry of Public Health and Sanitation, M.o.M.S., *NATIONAL GUIDELINES FOR THE DIAGNOSIS, TREATMENT AND PREVENTION OF MALARIA IN KENYA.* 2010.
36. de Oliveira, A.M., et al., *Performance of malaria rapid diagnostic tests as part of routine malaria case management in Kenya.* Am J Trop Med Hyg, 2009. **80**(3): p. 470-4.
37. Proux, S., et al., *Paracheck-Pf: a new, inexpensive and reliable rapid test for P. falciparum malaria.* Trop Med Int Health, 2001. **6**(2): p. 99-101.
38. Chandler, C.I., C.J. Whitty, and E.K. Ansah, *How can malaria rapid diagnostic tests achieve their potential? A qualitative study of a trial at health facilities in Ghana.* Malar J, 2010. **9**: p. 95.
39. Ruizendaal, E., et al., *Success or failure of critical steps in community case management of malaria with rapid diagnostic tests: a systematic review.* Malar J, 2014. **13**: p. 229.
40. Legese A. Mekuria, T.F.d.W., Nicole Spieker,Ramona Koech,Robert Nyarango,Stanley Ndwiga,Christine J. Fenenga,Alice Ogink,Constance Schultsz,Anja van't Hoog, *Analyzing data from the digital healthcare exchange platform for surveillance of antibiotic prescriptions in primary care in urban Kenya: A mixed-methods study.* Plos One 2019.
41. *Massive UHC Registration Drive to get underway in Kisumu County Kenya*. 2018 31 December 2019]; Available from: https://www.pharmaccess.org/update/massive-uhc-registration-drive-get-underway-kisumu-county-kenya/.

Figures

Figure 1.

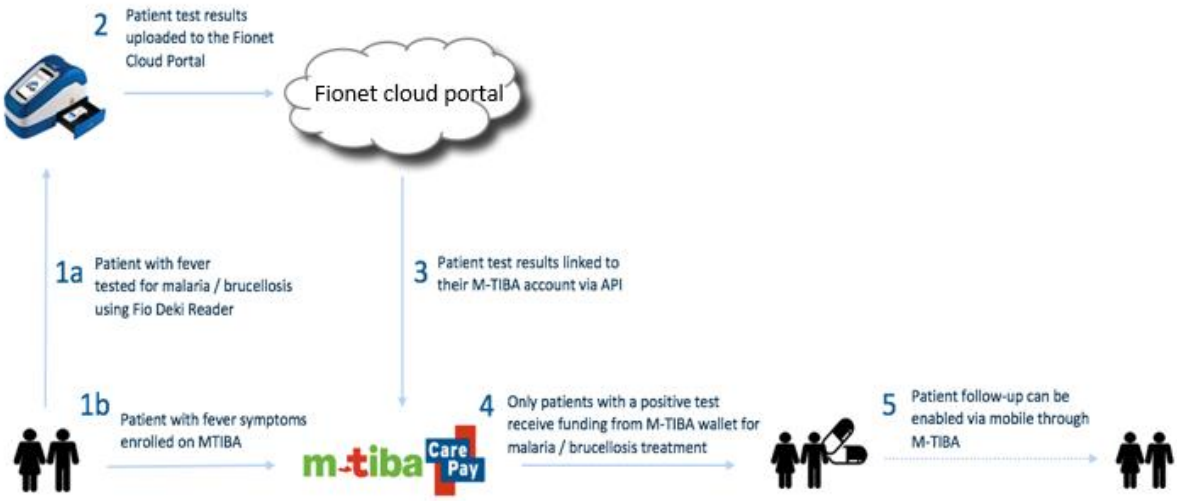

Figure 1. Schematic illustration ConnDx process. Step 1) Patient with fever symptoms is tested for malaria and enrolled on M-TIBA. 2) Test results of patient are uploaded to the cloud portal of Fionet. 3) The test results are also linked to the M-TIBA account of the patient. 4) Patients with a positive test receive funding for treatment. 5) Patient follow-up can be enabled via mobile through M-TIBA.

Figure 2.

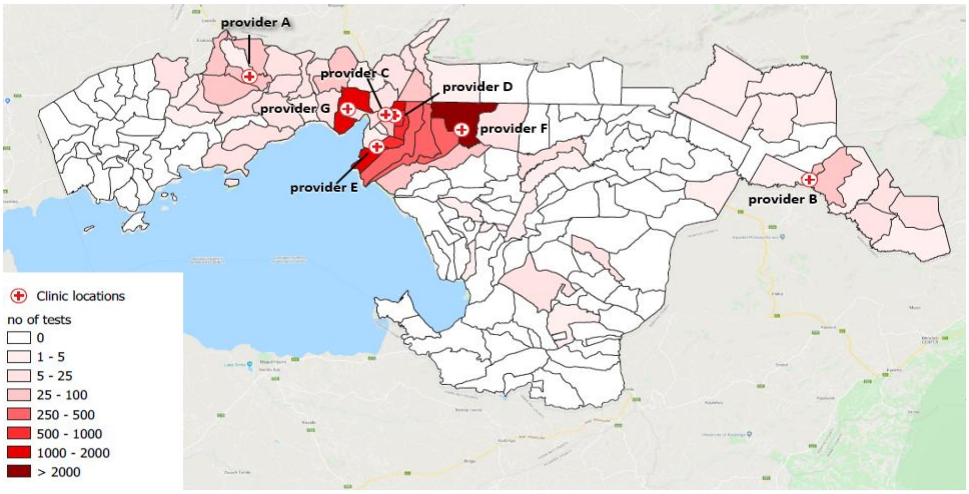

Figure 2. Location of the participating providers A-G in Kisumu County and hotspots of malaria tests. Data used to construct this map is gathered during this intervention.

Figure 3.

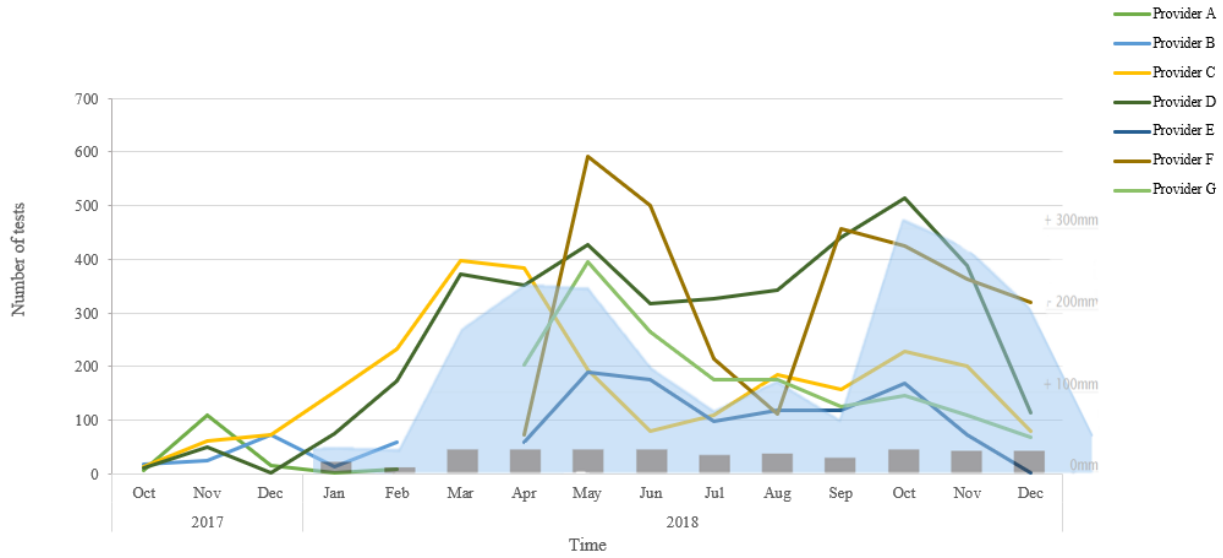

Figure 3. Participation dynamics providers A – G during the pilot of ConnDx in Kisumu. Number of transactions (tests) per provider from October 2017 – December 2018 derived from FIO database. Monthly rainfall in 2018 is indicated grey bars per months and in the light blue graph. Derived from worldweatheronline.com

Figure 4.

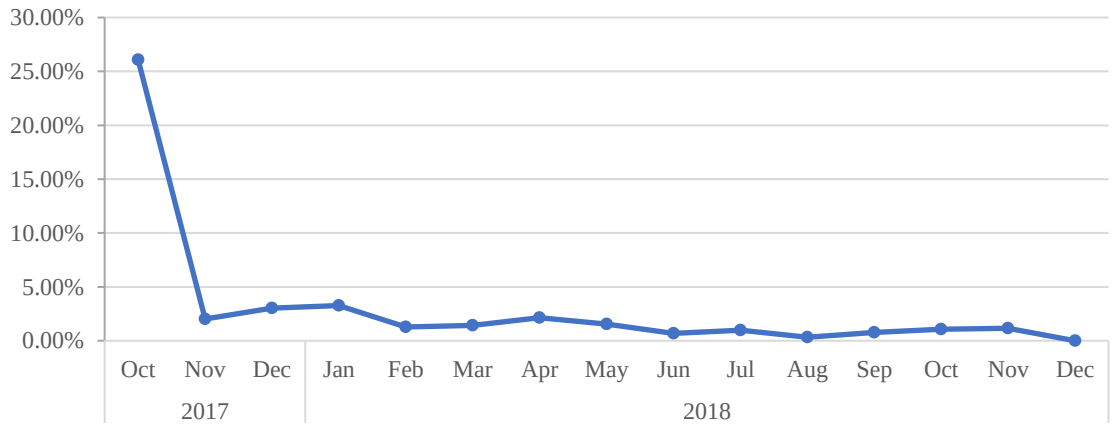

Figure 4a. Overall percentage of RDTs with errors, from October 2017 – December 2018

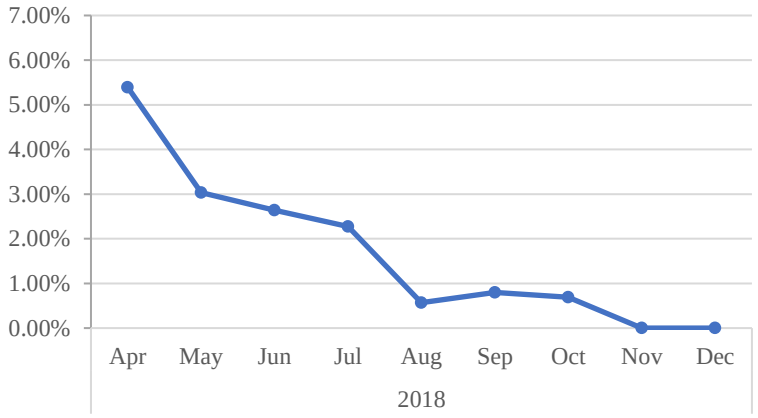

Figure 4b. Provider G percentage of RDTs with errors, from April 2018 – December 2018

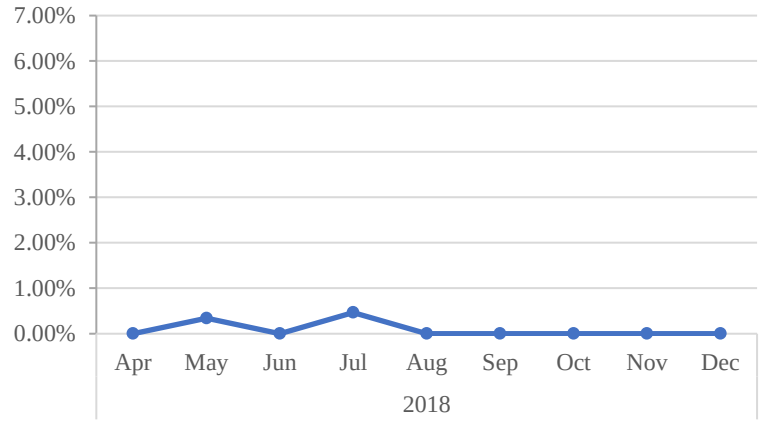

Figure 4c. Provider F percentage of RDTs with errors, from April 2018 – December 2018

Figure 5.

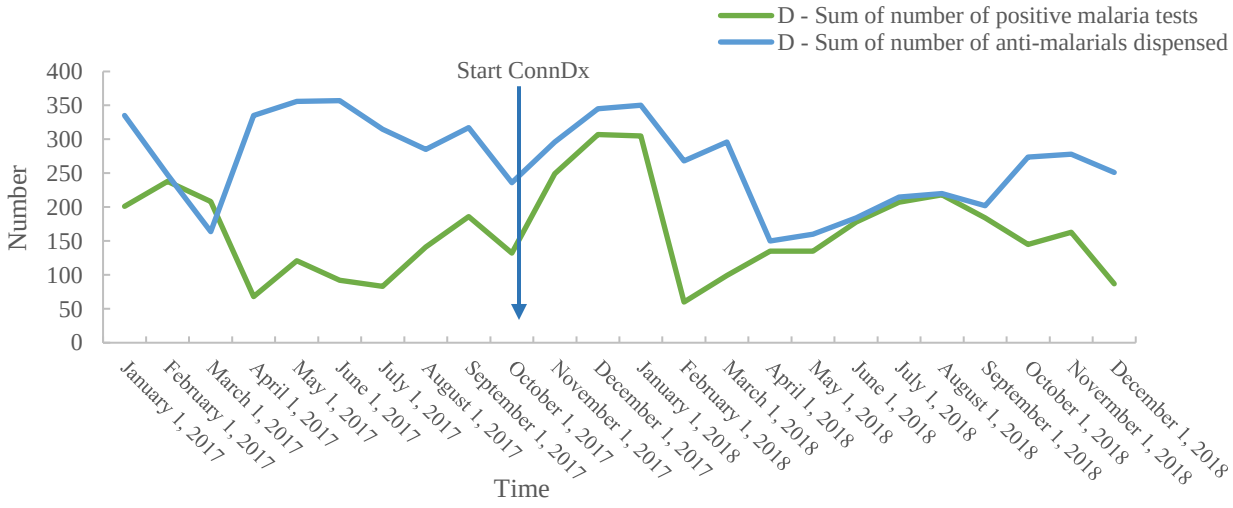

Figure 5. Number of positive malaria tests compared with number of antimalarials prescriptions dispensed within provider D throughout the project and the 9 months prior to implementation.

Figure 6.

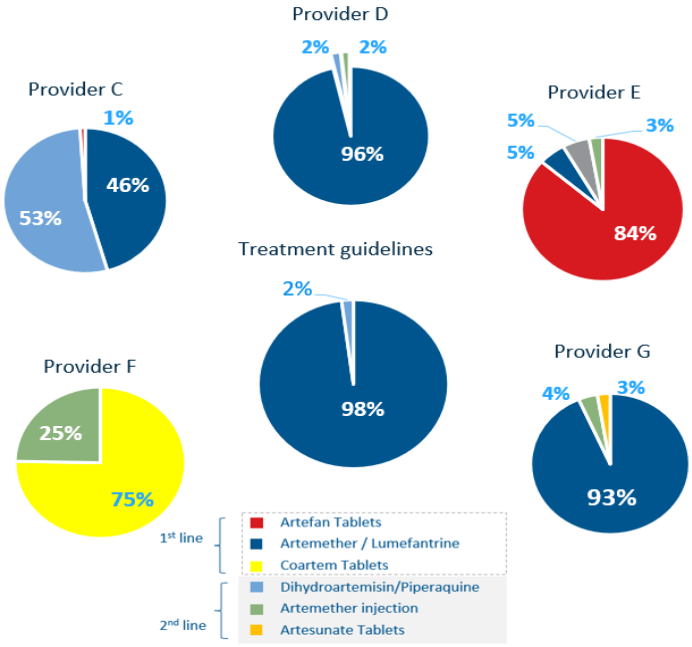

Figure 6. Type of antimalarials dispensed during ConnDx pilot per provider, divided in 1st versus 2nd line