

The impact of introducing malaria rapid diagnostic tests on fever case management: A synthesis of ten studies from the ACT Consortium

Running title: Impact of introducing malaria RDTs on fever case management

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Abstract

Since 2010, the World Health Organization recommends that all suspected cases of malaria be confirmed with parasite-based diagnosis before treatment. These guidelines represent a paradigm shift away from presumptive antimalarial treatment of fever. Malaria rapid diagnostic tests (mRDTs) are central to implementing this policy, intended to target artemisinin-based combination therapies (ACT) to patients with confirmed malaria and to improve management of patients with non-malarial fevers. The ACT Consortium conducted ten linked studies, eight in sub-Saharan Africa and two in Afghanistan, to evaluate the impact of mRDT introduction on case management across settings that vary in malaria endemicity and healthcare provider type. This synthesis includes 562,368 outpatient encounters (study size range 2400 to 432,513). mRDTs were associated with significantly lower ACT prescription (range 8-69% versus 20-100%). Prescribing did not always adhere to malaria test results; in several settings ACTs were prescribed to more than 30% of test-negative patients or to fewer than 80% of test-positive patients. Either an antimalarial or an antibiotic was prescribed for more than 75% of patients across most settings; lower antimalarial prescription for malaria test-negative patients was partly offset by higher antibiotic prescription. Symptomatic management with antipyretics alone was prescribed for fewer than 25% of patients across all scenarios. In community health worker and private retailer settings, mRDTs increased referral of patients to other providers. This synthesis provides an overview of shifts in case management that may be expected with mRDT introduction and highlights areas of focus to improve design and implementation of future case management programs.

117

118 **Introduction**

119 Providing appropriate antimalarial treatment to patients who have malaria has been a long-
120 standing challenge in fever case management, and has traditionally relied on presumptive symptom-
121 based diagnosis. Many people with malaria do not receive effective antimalarial medications,
122 increasing their risk of severe disease or death. At the same time, many of those who receive
123 antimalarials do not have malaria and are suffering from a non-malaria illness which may need
124 alternative treatment.¹ In order to improve rational use of artemisinin-based combination therapies
125 (ACTs), the World Health Organization (WHO) recommended in 2010 that all suspected cases of
126 malaria should have parasitological confirmation before treatment.^{2, 3} These changes represent a
127 paradigm shift from presumptive antimalarial treatment of fever to targeted use of ACTs only for
128 those with a positive malaria test.

129 Central to implementing this policy change are malaria rapid diagnostic tests (mRDTs),
130 relatively simple, inexpensive and reliable point-of-care tests that can be used where high-quality
131 microscopy services are not available.⁴ mRDTs are intended to improve the management of
132 suspected malaria cases, increasing the use of first-line antimalarials in patients with confirmed
133 malaria and encouraging the diagnosis and appropriate treatment of patients without malaria.¹
134 Following the WHO policy change, mRDT procurement has surged from 45 million tests globally in
135 2008 to 314 million in 2014.⁵ Parasite-based diagnosis prior to treatment is now policy in public
136 health facilities in most malaria-endemic countries, and mRDTs are also being introduced among
137 private retail and community health providers.^{6, 7, 8, 9, 10, 11, 12, 13, 14}

138 Clinical trials and early pilot projects prior to the widespread adoption of mRDTs supported
139 their use, though with some heterogeneity of results.¹⁵ Compared to presumptive treatment with
140 antimalarials, case management based on mRDTs generally reduced antimalarial prescription,

141 particularly in settings with relatively high provider adherence to test results and low malaria
142 prevalence.^{16, 17, 18, 19, 20, 21, 22} On the other hand, although provider adherence to negative mRDT
143 results was high in some studies,^{16, 17, 23, 24} it was low in others.^{25, 26, 27} Comparable data from good-
144 quality studies in a variety of contexts are needed in order to anticipate the effects of mRDT
145 implementation as these tests are rolled out at scale.

146 The ACT Consortium is a research partnership created to address key questions and inform
147 policy on ACT delivery.²⁸ The Consortium conducted studies in ten countries in Africa and Asia,
148 including ten studies specifically designed to address questions on improving the targeting of ACTs
149 through the use of mRDTs. These studies looked at the impact of mRDT introduction on fever case
150 management across a range of clinical and epidemiological contexts and among various types of
151 health care provider. Studies evaluated different mRDT intervention packages, leading to
152 heterogeneity that precludes formal meta-analysis. The current synthesis compares individual study
153 results to identify patterns across contexts and provide an overview of what may be expected from
154 mRDT implementation programs.

155 **Methods**

156 *Studies included in the analysis*

157 ACT Consortium studies were included in this analysis if they collected data on patient
158 consultations for suspected malaria, evaluated an intervention to implement mRDTs by health care
159 providers, and included a comparison group without the mRDT intervention. The ten studies
160 meeting these criteria are described in Table 1, including the abbreviation for each study used
161 throughout the text. All studies received ethical approval from their host academic institutions and
162 national authorities; see open-access publications for further details.^{29, 30, 31, 32, 33, 34, 35, 36, 37} (Leslie, T.
163 et al, in preparation) Data are available at the ACT Consortium data repository
164 (<https://actc.lshtm.ac.uk/>) or from the authors on request.

165 Eight studies took place in sub-Saharan Africa and two in Afghanistan, in a mix of rural and
166 urban settings. mRDTs were introduced in health facilities only (Afgh1, Cam1, Ghan1, Tanz1, Tanz2,
167 Uga1), among community health workers (Afgh2, Uga2), in private drug shops only (Uga3), or in a
168 combination of public facilities, private pharmacies, and drug shops (Nige1). Seven studies were
169 cluster-randomized trials of interventions to introduce mRDTs, two studies were individually-
170 randomized trials (Afgh1, Ghan1), and one study was a descriptive “before and after” evaluation
171 (Tanz1). All patients that were eligible in each study were included in the present analysis; typically
172 these were patients with suspected malaria, although one study included only children under age
173 five years (Uga2), and two studies collected data on all patient consultations (Tanz2, Uga1). Data
174 were collected using provider-completed records of treatments administered (Afgh1, Afgh2, Ghan1,
175 Uga1, Uga2), patient exit interviews (Tanz1), both of these methods (Cam1, Nige1, Tanz2), or
176 provider-completed records with follow-up interviews of a subsample of patients (Uga3).

177 From each study, “settings” and “scenarios” were identified for this analysis. Six studies
178 were conducted in multiple settings (indicated by suffix a, b, c), such as distinct geographical areas
179 and malaria transmission zones (Afgh1, Afgh2, Cam1, Tanz1, Uga2) or where providers used different
180 methods of routine malaria diagnosis (presumptive care or microscopy; Afgh1, Ghan1). Trial arms or
181 comparison groups within a setting were termed scenarios. All settings included at least one
182 scenario without mRDT interventions, and settings in three studies (Cam1, Nige1, Tanz2) included
183 multiple mRDT intervention scenarios. In total, the ten studies were conducted in 18 settings, with
184 18 scenarios without mRDT interventions and 24 scenarios with mRDT interventions.

185 Data were collected concurrently from scenarios with and without mRDT interventions in
186 seven studies. In three studies (Nige1, Tanz1, Tanz2) data from scenarios without mRDT
187 interventions were collected before mRDT introduction. The scale of the interventions and their
188 evaluations varied: for example, in Uga1 the intervention was implemented in ten health facilities,

189 and data were collected on 432,513 patient encounters in the study area; while Tanz1 evaluated a
190 nationwide intervention, and data were collected from 3,456 patients.

191 Microscopy was widely available in all settings in Cam1 and available at some higher-level
192 facilities in Tanz1, particularly in the Tanz1/c scenario without mRDT interventions. The two
193 individually randomized studies (Afgh1, Ghan1) took place both in settings where microscopy was
194 the standard practice and in settings where malaria diagnosis was symptom-based. Microscopy
195 services were non-existent or very limited in the other six studies (Afgh2, Nige1, Tanz2, Uga1, Uga2,
196 Uga3).

197 *Indicators of interest*

198 To examine the impact of mRDTs on patient care, malaria testing and prescribing indicators
199 were reviewed. Since the objective was to compare case management in areas with and without
200 mRDT interventions, our first indicator of interest was the proportion of patients tested by the
201 provider with any parasite-based diagnostic test (microscopy or mRDT). Prescribing indicators were
202 the proportions of patients prescribed one or more of the following medicines: ACTs, non-ACT
203 antimalarials, antibiotics (antibacterials), antifungals, antihelminthics and antipyretics. The
204 proportion of patients referred to another health care provider was also reviewed.

205 The ACT indicator was adjusted to account for malaria epidemiology and differences in first-
206 line antimalarial in two cases: In Afghanistan, *P. vivax* was treated with chloroquine and *P.*
207 *falciparum* with ACT; in these settings, the proportion of patients prescribed any antimalarial is
208 reported instead of ACT. In Nige1, prescription of SP and ACTs are reported for the scenario without
209 mRDT interventions, while only ACTs are reported for the scenarios with mRDT interventions. This
210 reflects a change in treatment between the 2009 scenario without mRDT interventions (when ACTs
211 were recommended but not yet widely used) and the 2011 scenarios with mRDT interventions
212 (when ACTs had largely replaced SP).

213 *Analytical approach*

214 Descriptive statistics on the indicators of interest were calculated from each scenario.
215 Estimates for each indicator were made for scenarios without mRDTs and those with mRDTs.
216 Prescribing indicators were further stratified by result of the diagnostic test performed by the health
217 care provider. Odds ratios and 95% confidence intervals for indicators of interest within each setting
218 were calculated using logistic regression with robust standard errors to account for clustering by the
219 primary unit of sampling or randomization (see Supplementary Tables). Formal meta-analysis was
220 deemed inappropriate due to heterogeneity of interventions evaluated and study contexts.
221 However, to aid comparisons between scenarios with and without mRDTs, the indicators of interest
222 are presented as graphic point estimates by study arm. The analysis was conducted in STATA 14
223 (STATA Corp LP, College Station, TX). Factors which may explain variations in mRDT use are
224 examined with additional qualitative data sources elsewhere.³⁸

225 **Results**

226 *Proportion of patients tested*

227 More patients were tested in scenarios where mRDTs had been introduced (Figure 1 and
228 Tables S1-S3). However, even with mRDTs available, the percentage of patients tested varied widely,
229 with 50% or fewer patients tested in five settings (Nige1, Tanz1/a, Tanz1/b, Tanz2, Uga1), and nearly
230 100% in others (Afgh2/a, Afgh2/b, Uga/2, Uga2/b, Uga3). The largest increases in proportion of
231 patients tested were seen where mRDTs were introduced outside of health facilities (Afgh2, Uga2,
232 Uga3). Similar proportions of children and adults were tested in most scenarios, but in Nige1,
233 Tanz1/a, and Uga1 test uptake was slightly higher for young children than for older patients. The
234 proportion of patients tested is not reported in Afgh1 or Ghan1, where patients were individually
235 randomized to mRDTs or microscopy (Afgh1/a, Afg1/b, and Ghan1/a), and to mRDTs or symptom-
236 based diagnosis (Afgh1/c and Ghan1/b).

237 Patients were also tested with microscopy in Cam1 and, to a lesser extent, in Tanz1. In
238 Cam1/a and Cam1/b, microscopy was common in all scenarios, and test use was not higher in
239 scenarios with mRDT interventions. In scenarios without mRDT interventions, 80% of patients were
240 tested with microscopy. In the four scenarios with mRDT interventions, 27% to 61% of patients were
241 tested with microscopy and 17% to 52% with mRDT (71% to 81% tested overall). Of the three Tanz1
242 settings, microscopy was most frequently used in the Tanz1/c scenario without mRDT interventions,
243 where 29% of patients were tested with microscopy and 2% with mRDT; in the corresponding
244 scenario with mRDT interventions, 8% were tested with microscopy and 63% with mRDT.

245 *Prescription of ACTs and other antimalarial medications*

246 Overall, mRDTs were associated with lower ACT prescribing (Figure 2a and Table S4). In
247 10/13 African settings, mRDT scenarios had statistically significantly lower ACT prescriptions than
248 scenarios without mRDT interventions. In two African settings, there was little difference between
249 mRDT and non-mRDT scenarios: Uga1, a high-transmission area where a high proportion of patients
250 required ACTs even after testing and Ghan1/a, where all non-mRDT patients were randomized to
251 testing with microscopy. In Nige1, where levels of testing were very low, presumptive diagnosis of
252 malaria was common even where mRDTs were available. Prescription of ACT or SP in the scenario
253 without mRDT interventions was similar to prescription of ACT in the three mRDT intervention
254 scenarios (around 50%). In 4/5 Afghanistan settings, prescription of any antimalarial was much lower
255 in scenarios with mRDT interventions than without; the exception was Afgh1/b, where (similar to
256 Ghan1/a) all non-mRDT patients were randomized to testing with microscopy, and where malaria
257 transmission was low.

258 Recorded prescription of non-ACT antimalarials (e.g. SP, quinine, oral artemisinin
259 monotherapies, etc.) was generally uncommon, except in Afghanistan. In 11/13 African settings,
260 non-ACTs were prescribed for fewer than 10% of patients both with and without mRDT interventions
261 (data not shown). Prescription of non-ACT antimalarials was higher in Cam1/b (20.9% in the scenario

262 without an mRDT intervention and approximately 15% in the two scenarios with mRDT
263 interventions) and in Nige1 (52.8% in the scenario without an mRDT intervention and approximately
264 30% in the three scenarios with mRDT interventions).

265 Overall, the finding of lower ACT prescription in scenarios with mRDT interventions was
266 mostly due to malaria test-negative patients not receiving ACTs (Figures 2b-d and Table S5). Fewer
267 than 30% of test-negative patients were treated with ACTs in most mRDT intervention scenarios;
268 exceptions were Cam1/a and Cam1/b, and Ghan1/a and Ghan1/b, where ACTs were prescribed for
269 39.2% to 49.1% of patients with negative malaria test results. There was no evident difference in this
270 indicator by test type; in the Cam1/a and Cam1/b scenarios with mRDT interventions, ACTs were
271 prescribed to 17.3% to 42.9% of microscopy test-negative patients and 15.6% to 45.9% of mRDT
272 test-negative patients (data not shown). The percentages of malaria test-positive patients in
273 scenarios with mRDT interventions who were prescribed ACTs ranged from 60.2% to 98.0% in 12/15
274 settings with data for this indicator. Prescription of ACTs to test-positive patients was over 90% in six
275 of these settings, but was just 60.2% to 81.2% in another six settings, with 69.4% to 96.2%
276 prescribed any antimalarial. In Tanz1/a, where stock-outs of ACTs in public health facilities were a
277 major problem, ACT prescribing for test-positive patients was 18.2%. In Afgh1/a and Afgh2/a, 99.5%
278 and 82.7% of test-positive patients were prescribed any antimalarial.

279 *Prescription of antibiotics*

280 In contrast to reduced ACT prescribing, the mRDT interventions were associated with
281 significantly more prescribing of systemic antibiotic (antibacterial) medications in seven settings
282 (Afgh1/c, Afgh2/a, Tanz1/a, Tanz1/b, Tanz1/c, Tanz2, Uga3) (Figure 3 and Tables S6-S7). In scenarios
283 with mRDT interventions, antibiotic prescribing patterns varied by mRDT result. In all settings except
284 Nige1, 40.0% to 79.9% of patients who tested negative for malaria were prescribed antibiotics.
285 Antibiotic prescription was similar in patients who were not tested. Among those with a positive
286 malaria test result, fewer than 45% were prescribed antibiotics, with higher proportions in Cam1/a

287 and Cam1/b. Prescription of *both* an antimalarial *and* a systemic antibiotic (Fig 4a and Table S8) was
288 relatively uncommon in all settings (<25% of patients, except in Cam1 and Afgh2/b) and was similar
289 or lower in scenarios with mRDT interventions. In contrast, the prescription of *either* an antimalarial
290 *or* an antibiotic medicine was high in all settings (more than 68%, except in Tanz1/a) and similar or
291 lower in scenarios with mRDT interventions (Figure 4b and Table S9). Further details of antibiotic
292 prescribing in ACT Consortium studies are presented elsewhere.³⁹

293 *Prescription of other medicines*

294 Data were recorded on prescription of other anti-infectives in some study settings.
295 Prescription of systemic antifungals (fluconazole, griseofulvin) was reported in five settings (Cam1/a,
296 Cam1/b, Ghan1/a, Ghan1/b and Uga1); the proportion of patients prescribed these medicines across
297 these settings was 2.6% or less (Table S10). Prescription of antihelminthics (albendazole,
298 mebendazole) was recorded in 13 settings (all study settings except those in Afgh2, Tanz2, and
299 Uga2); the proportion of patients prescribed these medicines ranged from 0.3% to 33.3%, which did
300 not appear attributable to whether the scenarios had an mRDT intervention or not (Table S10).

301 Prescription of antipyretic medicines alone, for symptomatic relief, without an antimalarial
302 or an antibiotic, ranged from 0.3% to 23.7% across all scenarios, and was similar or higher with
303 mRDT interventions except in Nige1 (Figure 4c and Table S11). Polypharmacy, defined as the
304 prescription of three or more medicines, varied widely across settings (Figure 4d). However, in most
305 settings polypharmacy was comparable with and without mRDT interventions, but was significantly
306 lower with mRDT interventions in four settings (Afgh1/b, Afgh2/a, Afgh2/b, Cam2/b (Figure 4d and
307 Table S12).

308 *Referral*

309 Figure 5 and Table S13 show the percentage of patients referred to another care provider or
310 facility. Referral was generally low across study settings. However, referral was significantly higher

311 with mRDT interventions among community health workers, particularly in Uga2/a, Uga2/b, and
312 Afgh2/b, and to a lesser extent in Uga3. Referral was uncommon (<5%) across all scenarios in studies
313 in public health facilities.

314 **Discussion**

315 Providing appropriate treatment to patients who present with malaria-like symptoms
316 remains a challenge in many endemic regions. This synthesis of data from ten ACT Consortium
317 studies illustrates the impact of mRDTs on case management. The data represent 24 scenarios
318 where mRDTs were introduced, compared with 18 scenarios without mRDT interventions. This
319 synthesis found that mRDT interventions reduced prescription of first-line antimalarials across
320 almost all settings, except where the tests were not often used. However, prescribing did not always
321 reflect test results: across a range of scenarios, ACTs were prescribed for some mRDT-negative cases
322 and, at least as concerning, ACTs were not prescribed for all mRDT-positive cases. The use of mRDTs
323 also influenced other treatment decisions, notably resulting in an increase of antibiotic prescription
324 especially for test-negative cases. Referral of patients to other health care providers was low across
325 nearly all settings, with a few specific exceptions discussed below.

326 What lessons can be learned from this synthesis, to inform expectations of programs that
327 implement mRDTs at scale? While mRDTs generally improve malaria case management, alone they
328 are not a panacea to solve the major challenge of effective fever management. Simply providing
329 mRDTs is insufficient if health workers continue prescribing antimalarials to test-negative patients²⁷,
330 ⁴⁰ or if alternative treatments are not appropriate. The ACT Consortium studies evaluated a range of
331 tailored and pre-tested elements as part of mRDT intervention strategies, such as enhanced provider
332 training or community awareness activities.^{41, 42} Anecdotally, interventions designed with more
333 intensive formative research led to greater reductions in ACT prescription for test-negative patients;
334 but such prescribing remained inappropriately high (10-49%).

335 Furthermore, in five of the eight African studies included in this analysis, more than 20% of
336 patients who tested positive for malaria at the point of care were not prescribed ACTs. Under-
337 treatment of malaria in settings where mRDTs have been implemented has been recognized in a
338 small proportion of cases (less than 5%), with few exceptions.^{43, 44, 45} However, results of this
339 synthesis suggest that under-treatment may be a more common problem than previously
340 recognized. The six settings with high ACT prescription for test-positive patients varied in terms of
341 malaria epidemiology, geography, and provider type; the same is true for the six settings with lower
342 ACT prescription for test-positive patients. To date, research into the reasons for this phenomenon
343 has been limited, although ACT Consortium study results presented elsewhere suggest that provider
344 motivations, stability of ACT supplies and pre-existing antimalarial preferences account for some of
345 this under-prescription.³⁸ Missed or ineffective treatment of malaria presents a risk to patients; a
346 balance between reducing unnecessary antimalarial use while ensuring ACTs are provided to all
347 malaria-positive cases needs to be integrated in future research, training, and implementation
348 programs.

349 This synthesis highlights the fact that effecting change in one health care practice can have
350 knock-on consequences for other practices. In many ACT Consortium studies, mRDT implementation
351 was associated with a higher level of antibiotic prescription, particularly for malaria test-negative
352 patients.³⁹ The proportion of patients prescribed *either* an antimalarial *or* an antibiotic was high, for
353 more than 75% of cases across most settings, and this was approximately similar in settings with and
354 without mRDT interventions. This suggests that in the absence of other diagnostic options,
355 presumptive antimalarial treatment may be exchanged for presumptive antibiotic treatment when
356 mRDTs are introduced. Many patients with uncomplicated febrile illness are likely to improve with
357 symptomatic management only (e.g. antipyretic), as noted in WHO case management guidelines;^{46, 47}
358 this approach was prescribed for just 0% to 24% of patients in ACT Consortium studies.
359 Inappropriate use of antimicrobials is of increasing global concern due to rising resistance, which can
360 result in longer illnesses, higher mortality, and increased treatment costs.^{48, 49} A more

361 comprehensive approach to case management is needed, rather than focusing on only a single
362 diagnosis and medication (e.g. malaria mRDTs and ACTs), if unintended consequences are to be
363 avoided.⁵⁰

364 Our data support the observation that introducing mRDTs may increase patient referral to
365 other health care providers, particularly among community health workers and private retailers.^{10, 51}
366 In particular, when a malaria test is negative, alternative diagnoses must be considered; the clinical
367 skills and diagnostic capacity to achieve this are limited among providers with less formal training, so
368 that referral may be necessary for adequate case management. Overall, referral remained
369 infrequent in ACT Consortium studies. Even when referral is recommended, patients are not always
370 inclined or able to follow the recommendation.^{52, 53, 54} If current recommendations to scale up
371 mRDTs in community and private health care settings are implemented, in order to improve referral
372 practices in a way that is safe for individual patients, and without unduly burdening other parts of
373 the health care system, the role of mRDTs will need to be better integrated into local pathways of
374 treatment-seeking and care provision.^{55, 56, 57}

375 The observed shifts in case management practices have cost implications for health systems
376 and for patients. When mRDTs lead to reductions in ACT use, there can be substantial savings in ACT
377 costs. However, additional costs are incurred for mRDT implementation: the tests themselves,
378 alternative treatments provided to mRDT-negative patients, additional referrals, and the activities
379 required for mRDT introduction, such as training, supervision, communication campaigns and quality
380 control. The overall cost impact in a given context will depend on several parameters, including the
381 relative cost of ACTs and mRDTs, the amount of subsidy for each, the proportion of patients tested,
382 the proportion who test positive, and provider adherence to test results. Analyses of the incremental
383 economic cost per fever case managed has been published for four studies included in this synthesis.
384 Where mRDTs were compared to microscopy (Afgh1, Ghan1, and Cam1), mRDTs were cost-saving or
385 costs were similar in Afghanistan⁵⁸, with an incremental provider cost per fever case managed

386 ranging from 0.20 to 1.11 USD in in Ghana⁵⁹ and Cameroon⁶⁰ (2011 USD). Where mRDTs were
387 compared with clinical diagnosis, the incremental provider cost per fever case managed ranged from
388 0.24 USD to 10.9 USD across different transmission levels and provider types in Afghanistan, Ghana,
389 and Uganda (2011 USD).^{58, 59, 61} These incremental costs may be considered good value for money if
390 they lead to sufficient improvements in health outcomes. A full consideration of cost-effectiveness
391 would require costs from both health sector and household perspectives, extrapolation to final
392 health outcomes such as cost per death or disability adjusted life year (DALY) averted, and sensitivity
393 analyses to explore the impact of variation in prescribing and referral practices. Ideally a full analysis
394 should also include the impact of malaria testing on enhancing malaria surveillance systems and
395 resulting improvements in targeting of malaria interventions.

396 The present analysis was subject to several limitations. Data were collected concurrently
397 from scenarios with and without mRDT interventions in seven studies, while in the other three
398 (Nige1, Tanz1, and Tanz2) data were collected before and after mRDT introduction (Table 1). In
399 Nige1, the interval between the two data collection points corresponded with a shift in antimalarial
400 use from SP to ACT; while ACT prescription decreased, any antimalarial prescription remained high
401 ($\geq 75\%$). In addition, some indicators varied in availability and precise definition across studies (see
402 footnotes to Figures and Supplementary Tables.) For example, in Uga2, prescription of antibiotics
403 and polypharmacy were not reported because community health workers were only permitted to
404 dispense antimalarials and antipyretics. In Tanz1, data on medicines prescribed were not available
405 from scenarios without mRDTs, so data on medicines dispensed were used for all Tanz1 scenarios. In
406 designing the ACT Consortium studies and mRDT implementation packages, investigators sought to
407 accommodate varied and transitioning contexts, while still obtaining data that could be compared
408 across studies. This synthesis therefore did not aim to provide combined estimates of the size of
409 effect of the impact of mRDTs (meta-analysis). Instead, comparison of findings from the individual
410 studies identified clear patterns across diverse geographical, epidemiological, and health sector
411 contexts, indicating both robustness and generalizability of the results.

412 In summary, evidence from ten ACT Consortium studies demonstrates that mRDT
413 introduction can reduce prescription of ACTs. However, mRDTs are not an easy technological fix.
414 Critically, challenges exist in ensuring that all patients who test positive for falciparum malaria are
415 prescribed ACT; anything less endangers individual patients and the credibility of programs. It is also
416 necessary to ensure that patients who test negative receive appropriate management, which may or
417 may not include other antimicrobials. ACT Consortium studies were conducted between 2007 and
418 2013, and since that time mRDT implementation programs continue to evolve. These combined
419 results provide an overview of the generally positive shifts in case management that may be
420 expected with mRDT introduction, and highlight issues that warrant particular attention in future
421 work on point-of-care diagnosis and fever and malaria case management.

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