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Predictive Performance of Rapid Diagnostic Tests for Falciparum Malaria and Its Modeled Impact on Integrated Community Case Management of Malaria in Sub-Saharan African Febrile Children

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(See the Editorial Commentary by Petersen and Grobusch on pages e1168–9.)

Background. Integrated community case management (iCCM) of malaria complements public health services to improve access to timely diagnosis and treatment of malaria. ICCM relies on standardized test-and-treat algorithms implemented by community health workers using malaria rapid diagnostic tests (RDTs). However, due to a changing epidemiology of fever causes in Africa, positive RDT results might not correctly reflect malaria. In this study, we modeled diagnostic predictive values for all malaria-endemic African regions as an indicator of the programmatic usefulness of RDTs in iCCM campaigns on malaria.

Methods. Positive predictive values (PPVs) and negative predictive values (NPVs) of RDTs for clinical malaria were modeled. Assay-specific performance characteristics stem from the Cochrane Library and data on the proportion of malaria-attributable fevers among African febrile children aged <5 years were used as prevalence matrix.

Results. Average country-level PPVs vary considerably. Ethiopia had the lowest PPVs (histidine-rich protein II [HRP2] assay, 17.35%; parasite lactate dehydrogenase [pLDH] assay, 39.73%), and Guinea had the highest PPVs (HRP2 assay, 95.32%; pLDH assay, 98.46%). On the contrary, NPVs were above 90% in all countries (HRP2 assay, ≥94.87%; pLDH assay, ≥93.36%).

Conclusions. PPVs differed considerably within Africa when used to screen febrile children, indicating unfavorable performance of RDT-based test-and-treat algorithms in low-PPV settings. This suggests that the administration of antimalarials alone may not constitute causal treatment in the presence of a positive RDT result for a substantial proportion of patients, particularly in low-PPV settings. Therefore, current iCCM algorithms should be complemented by information on other setting-specific major causes of fever.

Keywords. malaria; RDT; integrated community case management; Africa.

In the past decade, community management approaches of malaria have become a cornerstone of various national programs on malaria case management and malaria control [1, 2]. Such approaches are centered on residents of a given community and usually complement the existing higher levels of healthcare infrastructure (eg, district-level hospitals, healthcare units). They entail recruitment and training of health workers who operate on the community level and thereby involve an increased accessibility of healthcare to the target population. There is diversity in how community-based approaches deliver care to the local population, ranging from home treatment approaches to offering adequate treatment at easily accessible focal points (eg, pharmacies, churches, schools) [1, 2]. Therefore, community health workers do not only bridge the gap between the formal healthcare system and the affected population, they also maintain some operational independence. Often, community management approaches are based on simple and clear algorithms to be followed by the community health worker on how to diagnose and treat malaria and when to refer a person to a higher level of the healthcare system [1]. In an attempt to simultaneously fight several major causes of childhood morbidity and mortality (ie, most prominently pneumonia, diarrhea, and malaria) in lower- and middle-income countries, the World Health Organization (WHO) and UNICEF endorsed integrated community case management (iCCM) programs [3].

Malaria Rapid Diagnostic Tests

It is a WHO-endorsed policy that administration of antimalarial medication is preceded by a positive diagnostic test result

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for malaria [4]. Whereas microscopic detection of *Plasmodium* spp. in peripheral blood remains the gold standard diagnostic for case management, rapid diagnostic tests (RDTs) have increasingly become the backbone of malaria diagnostics in many malaria-endemic lower- and middle-income countries [5, 6]. RDTs detect parasite-specific antigens in peripheral blood, such as histidine-rich protein II (HRP2) and parasite lactate dehydrogenase (pLDH) [7]. Diagnostic performance characteristics of RDTs to detect malaria were assessed systematically and described as favorable with sensitivities and specificities above 90% in malaria-endemic settings [8]. As part of iCCM programs, it is recommended that all febrile children with malaria be tested with a RDT and that a dose of an effective antimalarial drug be administered in the presence of a positive RDT result [3, 4].

Importance of Diagnostic Predictive Values

Not every positive diagnostic test result truly indicates the presence of disease [9]. The validity of diagnostic test results does not only depend on assay-specific characteristics of a diagnostic tool but also relies on the prevalence of the condition of interest in the target population. The concept of predictive values combines assay-specific properties with properties of the respective target population [10]. The positive predictive value (PPV) indicates the probability of true disease in the presence of a positive diagnostic test result, and the negative predictive value (NPV) indicates the probability of absence of disease in the presence of a negative diagnostic test result. Therefore, predictive values provide more useful information for malaria case management algorithms on the community level than the assay-specific properties of sensitivity and specificity.

As the transmission intensity of malaria affects the predictive performance of diagnostic test results, it is not understood how predictive values of malaria RDTs vary within sub-Saharan Africa [11, 12]. This understanding is of importance to tailor test-and-treat algorithms of iCCM programs of malaria in respective regions. In this study, we modeled predictive values of RDTs to detect clinical malaria in children aged <5 years in malaria-endemic regions in Africa. Based on this assessment, we evaluated the predictive values as a proxy measure to estimate the effectiveness of current malaria RDT-based algorithms for the management of febrile children in iCCM programs.

METHODS

Computation of Predictive Values

Values for sensitivity and specificity were extracted from a meta-analysis that evaluated diagnostic RDT performance to diagnose falciparum malaria in endemic settings using expert light microscopy as the gold standard [8]. The meta-analysis included 84 studies that assessed the performance characteristics of HRP2-based assays and 20 studies that assessed pLDH-based assays. HRP2-based RDTs have shown sensitivities and specificities of about 95.0% (95% confidence interval [CI], 93.5%–96.2%) and 95.2% (95% CI, 93.4%–99.4%), respectively, to diagnose falciparum malaria in endemic populations; respective performance of pLDH-based RDTs are 93.2% (95% CI, 88.0%–96.2%) and 98.5% (95% CI, 96.7%–99.4%) [8]. To date and to the best of our knowledge, this study constitutes the best available evidence for conventional RDT performance in endemic settings. Regions other than Africa and *Plasmodium* species other than *Plasmodium falciparum* were not considered in this analysis. Predictive values were ascertained via formulae according to Altman and Bland (Supplementary Material) [9].

Both predictive values have a dependency on the prevalence of the condition that they aim to detect [9, 10]. PPVs decrease as the prevalence decreases, while NPVs decrease as the prevalence increases. Both PPVs and NPVs depend on sensitivity and specificity; however, PPVs are especially impaired by low specificities and NPVs by low sensitivities (Supplementary Figures 1 and 2).

Standardized Malaria Prevalence Data From Malaria Atlas Project

The Malaria Atlas Project (Big Data Institute, University of Oxford, United Kingdom) constitutes a public and freely accessible database with epidemiological data related to malaria in Africa [13]. It allows visualization of data in a cartesian coordinate system (heat map) with a granularity of 5 km × 5 km geographical area. Data were downloaded from the Malaria Atlas Project for malaria-endemic African countries on the "proportion of malaria-attributable fever among ≤ five-year-old children with fever (MAF)" [11]. These data indicate the number of febrile episodes and its attributable fraction to malaria.

Modeling and data visualization were performed in R Statistic 3.5.1 (R Project, University of Auckland, New Zealand) using a dedicated R package that facilitates access to Malaria Atlas Project databases [14]. The predictive performance of RDTs was modeled on the basis of MAF and visualized as heat maps to highlight disparities of performance in the greatest detail possible. Favorable RDT performance was highlighted in green and unfavorable RDT performance in red; yellow is in between the 2 extremes of green and red. A high proportion of MAF was allocated the color red and a low proportion of MAF the color blue. STATA/SE 15.1 (StataCorp) was used to create the Supplementary Figures, allowing the depiction of scenarios of changing MAF prevalence or changing RDT performance characteristics.

Interpretability of Predictive Performance of MAF Models

The "proportion of malaria-attributable fever among ≤ five-year-old children with fever" (ie, the MAF dataset available in the Malaria Atlas Project) was computed based on primary data from cross-sectional national household surveys conducted among children aged ≤5 years in African countries in 2014. As

Table 1. Average Predictive Values per Country

Country	Proportion of Malaria-Attributable Fever Among Febrile Children Aged ≤5 Years, %	Histidine-Rich Protein II–based RDT		Parasite Lactate Dehydrogenase–based RDT	
		PPV% (95% CI)	NPV% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
Angola	8.26	64.05 (56.05–93.52)	99.52 (99.37–99.65)	84.83 (70.59–93.52)	99.38 (98.89–99.65)
Benin	18.69	81.97 (76.5–97.35)	98.8 (98.42–99.12)	93.45 (85.97–97.35)	98.43 (97.22–99.12)
Botswana	1.28	20.42 (15.51–67.52)	99.93 (99.9–99.95)	44.61 (25.69–67.52)	99.91 (99.83–99.95)
Burkina Faso	15.82	78.81 (72.69–96.78)	99.02 (98.7–99.28)	92.11 (83.36–96.78)	98.71 (97.72–99.28)
Burundi	7.86	62.8 (54.72–93.18)	99.55 (99.4–99.67)	84.12 (69.46–93.18)	99.41 (98.95–99.67)
Cameroon	19.71	82.93 (77.66–97.52)	98.72 (98.32–99.07)	93.84 (86.74–97.52)	98.33 (97.04–99.07)
Central African Republic	27.99	88.49 (84.63–98.42)	97.99 (97.36–98.53)	96.02 (91.2–98.42)	97.38 (95.39–98.53)
Chad	7.35	61.09 (52.91–92.71)	99.58 (99.45–99.69)	83.13 (67.9–92.71)	99.45 (99.02–99.69)
Congo	17.94	81.22 (75.59–97.22)	98.86 (98.5–99.17)	93.14 (85.35–97.22)	98.51 (97.35–99.17)
Côte d'Ivoire	22.42	85.11 (80.36–97.88)	98.5 (98.02–98.9)	94.72 (88.51–97.88)	98.04 (96.53–98.9)
Democratic Republic of the Congo	14.78	77.43 (71.07–96.52)	99.09 (98.8–99.34)	91.5 (82.22–96.52)	98.81 (97.89–99.34)
Djibouti	3.63	42.7 (34.79–85.79)	99.8 (99.73–99.85)	70.06 (50.11–85.79)	99.74 (99.53–99.85)
Equatorial Guinea	41.44	93.33 (90.92–99.12)	96.41 (95.3–97.36)	97.77 (94.96–99.12)	95.34 (91.92–97.36)
Eritrea	6.14	56.42 (48.09–91.29)	99.65 (99.54–99.75)	80.25 (63.56–91.29)	99.55 (99.19–99.75)
Ethiopia	1.05	17.35 (13.06–62.98)	99.94 (99.92–99.95)	39.73 (22.05–62.98)	99.92 (99.86–99.95)
Gabon	9.96	68.64 (61.04–94.66)	99.42 (99.23–99.57)	87.29 (74.68–94.66)	99.24 (98.64–99.57)
Gambia	2.05	29.28 (22.86–77.04)	99.89 (99.85–99.92)	56.52 (35.81–77.04)	99.85 (99.74–99.92)
Ghana	30.4	89.63 (86.08–98.59)	97.75 (97.04–98.35)	96.44 (92.09–98.59)	97.07 (94.85–98.35)
Guinea	50.74	95.32 (93.58–99.39)	94.86 (93.31–96.21)	98.46 (96.48–99.39)	93.36 (88.66–96.21)
Guinea-Bissau	13.7	75.85 (69.22–96.21)	99.17 (98.9–99.39)	90.79 (80.89–96.21)	98.91 (98.06–99.39)
Kenya	2.22	31 (24.33–78.44)	99.88 (99.84–99.91)	58.51 (37.71–78.44)	99.84 (99.71–99.91)
Liberia	13.48	75.51 (68.82–96.15)	99.18 (98.92–99.4)	90.63 (80.6–96.15)	98.93 (98.1–99.4)
Madagascar	8.49	64.74 (56.79–93.7)	99.51 (99.35–99.64)	85.21 (71.21–93.7)	99.36 (98.86–99.64)
Malawi	14.16	76.55 (70.03–96.35)	99.14 (98.86–99.37)	91.11 (81.47–96.35)	98.87 (97.99–99.37)
Mali	12.59	74.03 (67.11–95.84)	99.24 (99–99.45)	89.94 (79.34–95.84)	99.01 (98.24–99.45)
Mauritania	2.61	34.65 (27.51–81.12)	99.85 (99.81–99.89)	62.47 (41.67–81.12)	99.81 (99.66–99.89)
Mozambique	35.88	91.71 (88.79–98.89)	97.14 (96.25–97.9)	97.2 (93.71–98.89)	96.28 (93.5–97.9)
Namibia	2.64	34.92 (27.75–81.29)	99.85 (99.81–99.89)	62.75 (41.96–81.29)	99.81 (99.66–99.89)
Niger	4.82	50.05 (41.77–89.03)	99.73 (99.64–99.8)	75.88 (57.45–89.03)	99.65 (99.37–99.8)
Nigeria	13.45	75.46 (68.76–96.14)	99.19 (98.93–99.4)	90.61 (80.56–96.14)	98.93 (98.1–99.4)
Rwanda	6.98	59.76 (51.52–92.32)	99.6 (99.48–99.71)	82.33 (66.67–92.32)	99.48 (99.07–99.71)
Senegal	4.32	47.19 (39.01–87.86)	99.76 (99.68–99.82)	73.72 (54.62–87.86)	99.68 (99.44–99.82)
Sierra Leone	20.18	83.34 (78.17–97.59)	98.68 (98.27–99.04)	94.01 (87.08–97.59)	98.28 (96.95–99.04)
Somalia	8.8	65.63 (57.75–93.92)	99.49 (99.33–99.63)	85.7 (72.01–93.92)	99.33 (98.81–99.63)
South Africa	6.58	58.22 (49.94–91.86)	99.63 (99.51–99.73)	81.39 (65.25–91.86)	99.51 (99.13–99.73)
South Sudan	13.15	74.97 (68.2–96.04)	99.21 (98.95–99.42)	90.39 (80.14–96.04)	98.96 (98.15–99.42)
Sudan	3.86	44.27 (36.25–86.55)	99.78 (99.72–99.84)	71.38 (51.7–86.55)	99.72 (99.5–99.84)
Swaziland	4.11	45.89 (37.78–87.29)	99.77 (99.7–99.83)	72.7 (53.33–87.29)	99.7 (99.47–99.83)
Tanzania	10.64	70.2 (62.78–95.02)	99.37 (99.17–99.54)	88.09 (76.04–95.02)	99.18 (98.54–99.54)
Togo	26.41	87.65 (83.56–98.29)	98.14 (97.56–98.64)	95.7 (90.53–98.29)	97.58 (95.73–98.64)
Uganda	10.06	68.88 (61.3–94.71)	99.41 (99.22–99.57)	87.42 (74.89–94.71)	99.23 (98.63–99.57)
Zambia	20.52	83.63 (78.52–97.64)	98.66 (98.23–99.02)	94.13 (87.31–97.64)	98.24 (96.89–99.02)
Zimbabwe	4.48	48.13 (39.91–88.26)	99.75 (99.67–99.82)	74.45 (55.56–88.26)	99.67 (99.42–99.82)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; RDT, rapid diagnostic test.

part of these surveys, information on history of fever within the last 2 weeks was captured and a *P. falciparum*-specific RDT was performed in every child [11]. This information allowed the authors of the MAF dataset to compute the proportion of fevers among children aged ≤5 years at the community level that are truly attributable to malaria (as opposed to children who are febrile due to other infections or other medical conditions, while at the same time harboring an asymptomatic concomitant *Plasmodium* infection).

If MAF data are used as prevalence matrix and combined with meta-analytic performance characteristics of malaria RDTs, the resulting predictive values demonstrate the probabilities that

malaria is causally responsible (PPV) and not causally responsible (NPV) for fever in young febrile children in a malaria-endemic African community. Assuming that every child with a positive RDT receives an effective dose of artemisinin-combination therapy according to WHO guidelines, PPVs further constitute a proxy for appropriate (ie, causal) fever case management on the community level in malaria-endemic regions of Africa and provides a direct indication of over- or undertreatment of malaria based on the algorithm used [5].

RESULTS

MAF Values

MAF data were available for 43 malaria-endemic countries of Africa (Table 1, Figure 1). There were 20.9% (9 of 43) of countries with a MAF value of at least 20%; 30.2% (13 of 43) of countries had a MAF value between 10% and 19.9% and 48.8% (21 of 43) of countries had a MAF value below 10%.

Positive Predictive Values

Average PPVs were highest in countries with high MAF values and lowest in countries with low MAF values for both HRP2-based and pLDH-based assays; the respective distribution is depicted in Figures 2 and 4. Twelve of 43 (27.9%) countries had average HRP2 assay-based PPVs above 80% and 7.0% (3 of 43) had PPVs of at least 90% (Table 1); 37.2% (16 of 43) of countries had HRP2 assay-based PPVs between 60% and 79.9%, 20.9% (9 of 43) between 40% and 59.9%, and 14.0% (6 of 43) below 40%. Ethiopia had the lowest average HRP2 assay-based PPV at 17.35%. For iCCM programs in which each positive HRP2-based RDT result in a febrile child is followed by antimalarial treatment, findings suggest that in 11 (25.6%; 11

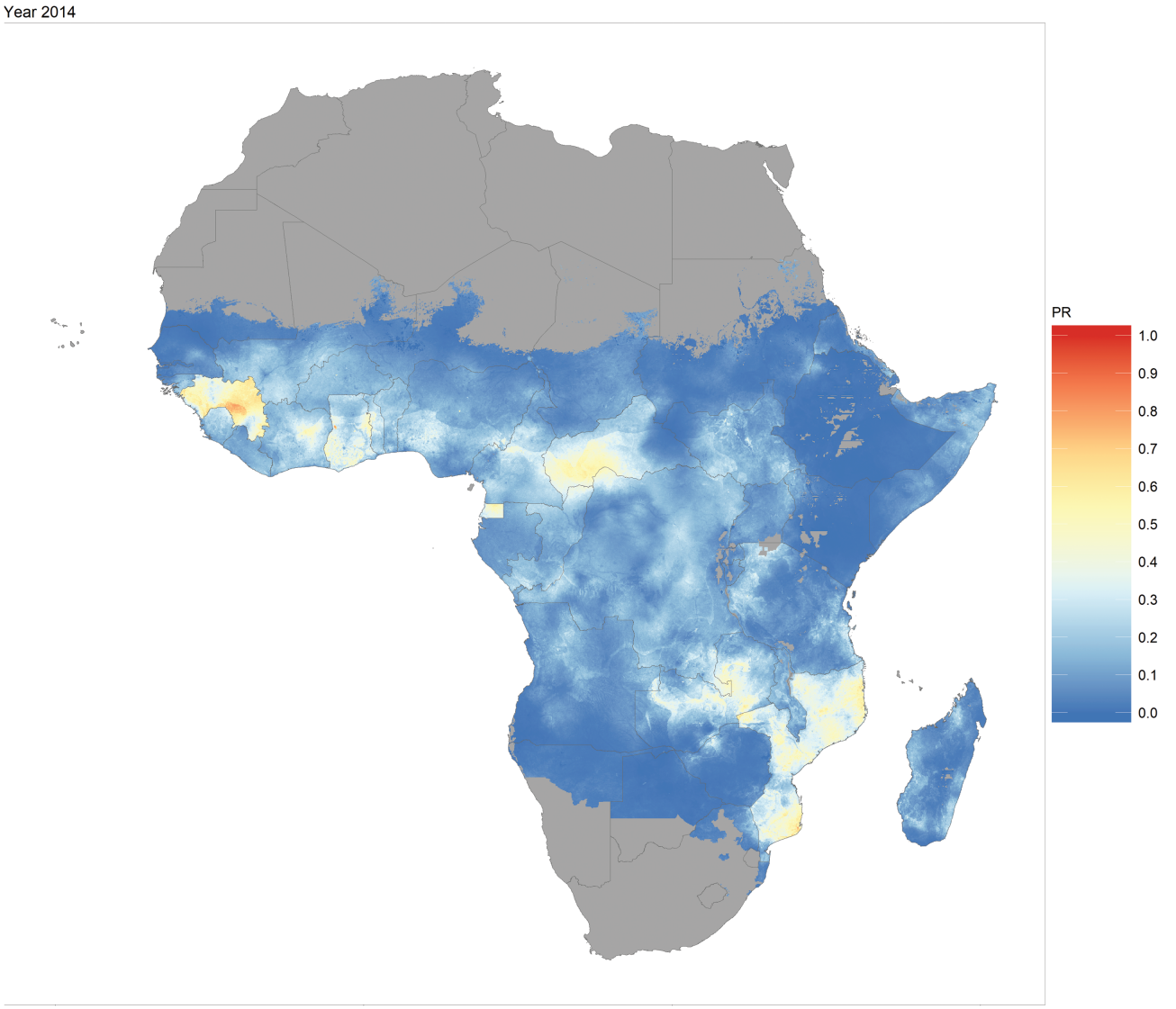

Figure 1. Proportion of malaria-attributable fevers among all febrile children aged ≤5 years. Abbreviation: PR, prevalence.

of 43) countries, less than 50% of children treated with antimalarials would have received causal treatment of their febrile condition. Concordantly, HRP2-based RDT test-and-treat algorithms would lead to inappropriate diagnoses and eventually noncausative treatment in at least 50% of febrile children in these 11 countries.

Thirty-one of 43 (72.1%) countries had average pLDH assay-based PPVs above 80% and 44.2% (19 of 43) had PPVs of at least 90%. There were 18.6% (8 of 43) of countries with pLDH assay-based PPVs between 60% and 79.9%, 7.0% (3 of 43) between 40% and 59.9%, and 2.3% (1 of 43) below 40%. Ethiopia had the lowest average pLDH assay-based PPV at 39.73%. Again, for iCCM programs in which each positive pLDH-based RDT in a febrile child is followed by antimalarial treatment, findings suggest that in only 2 (4.7%; 2 of 43) countries, adequate diagnosis and causal treatment was given in less than 50% of febrile children. Concordantly, pLDH-based RDT test-and-treat algorithms would lead to misclassification and potential noncausative treatment of at least 50% of febrile children in these 2 countries.

Negative Predictive Values

Concordantly, average NPVs were lowest in countries with high MAF values and highest in countries with low MAF values (Figures 3 and 5). There were 72.1% (31 of 43) of countries with average HRP2 assay-based NPVs above 99.0% and 97.7% (42 of 43) with an NPV above 95.0% (Table 1). Guinea had the lowest average HRP2 assay-based NPV with 94.86%. Twenty-four of 43 (55.8%) countries had average pLDH assay-based NPVs above 99.0% and 97.7% (42 of 43) had an NPV above 95.0%. Guinea had the lowest average pLDH assay-based NPV with 93.36%.

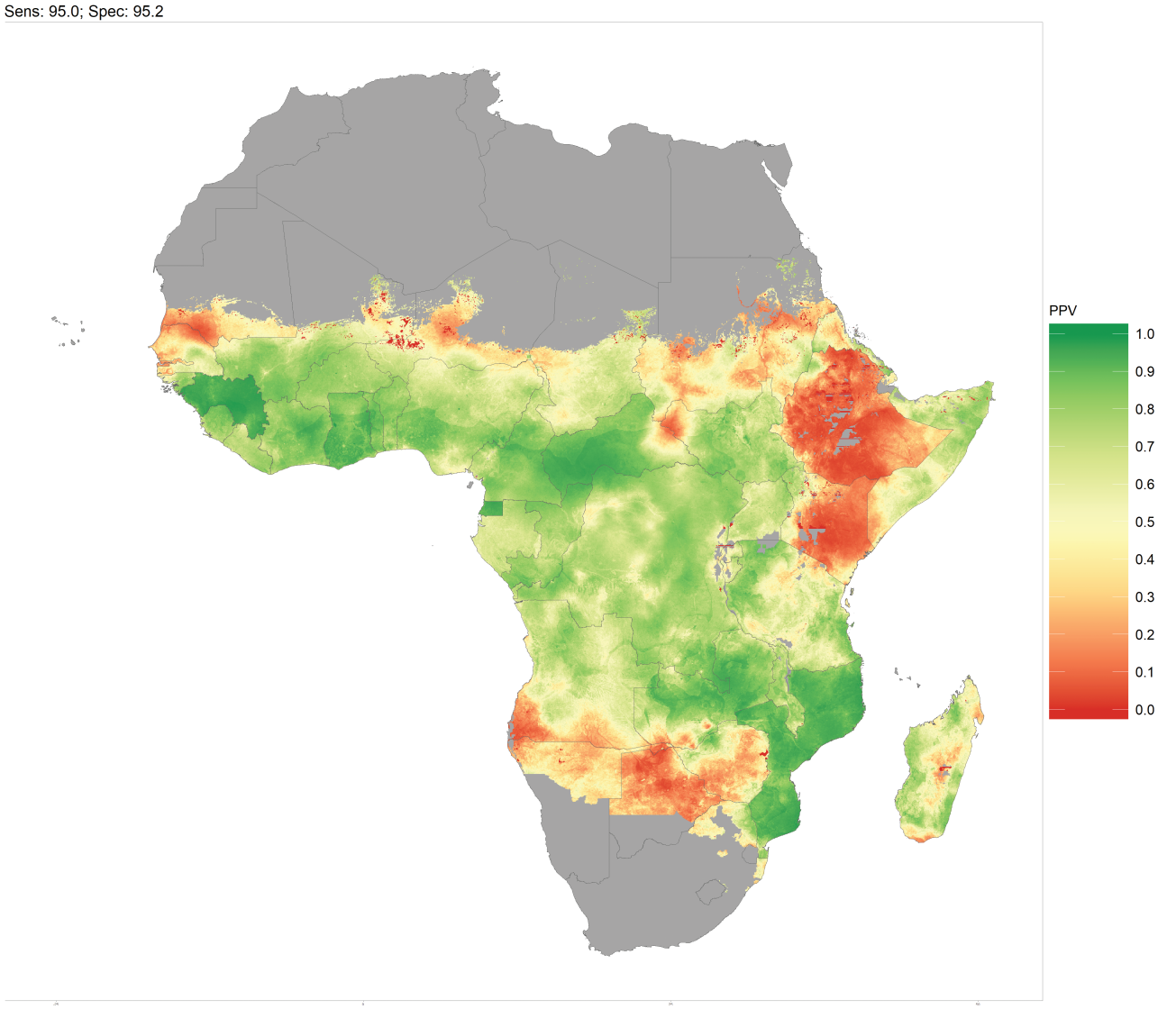

Figure 2. Histidine-rich protein II–based malaria rapid diagnostic tests. PPVs reflect the probability of malaria as the causal reason for fever in the presence of a positive test result in children aged ≤5 years. Probability measure from 0 to 1. Abbreviations: PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Assuming that each negative test result leads to no antimalarial treatment, undertreatment is estimated to occur in less than 5% of febrile children in all observed countries, except for Guinea, where undertreatment of febrile children was estimated to be 5.14% for HRP2-based test-and-treat algorithms and 6.64% for pLDH-based algorithms.

DISCUSSION

In iCCM programs, common life-threatening conditions in children, such as pneumonia, diarrhea, and malaria, are managed early on at the community level by community health workers with basic medical training [3, 5]. With the advent of more sensitive and specific malaria RDTs, initially simple case management algorithms received an additional layer of complexity, namely, that effective antimalarials should only be administered in the presence of a positive malaria RDT result [3, 15]. Therefore, the presented predictive values hold great importance for official iCCM programs as they estimate the validity of respective RDT-based test-and-treat algorithms. Importantly, PPVs rely on malaria transmission intensity, which consecutively affects MAF data. To ensure up-to-date estimates of PPVs, it is recommended that MAF data be produced periodically and be publicly accessible. This may ultimately have an impact on treatment algorithms of iCCM programs. It is of note that our focus here is on *P. falciparum*; therefore, its generalizability will likely not extend to regions of high *Plasmodium vivax* endemicity, such as regions in East Africa (eg, Ethiopia).

Overall NPVs were highly favorable for both HRP2-based and pLDH-based assays and for virtually all malaria-endemic

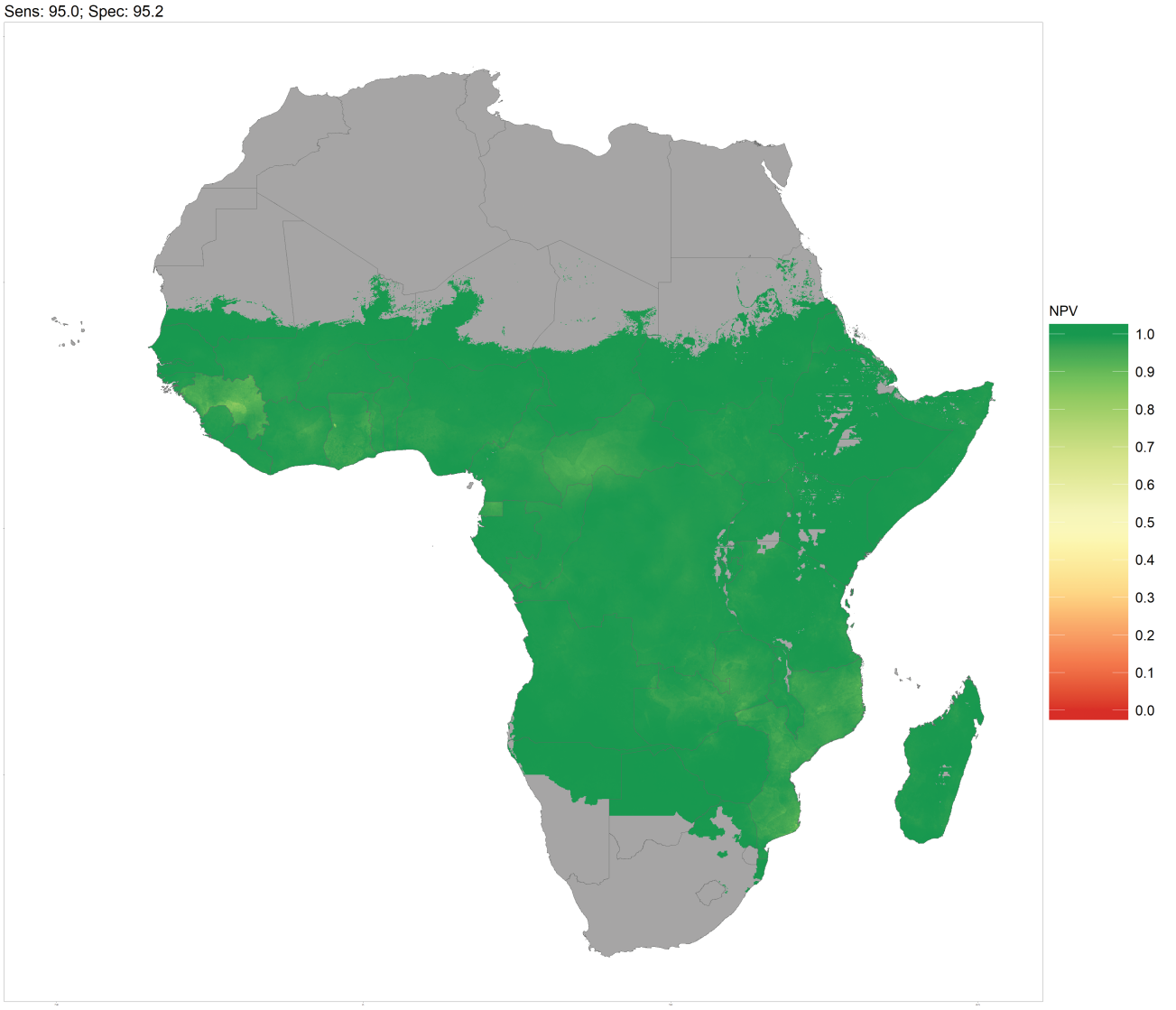

Figure 3. Histidine-rich protein II–based malaria rapid diagnostic tests. NPVs reflect the probability that malaria is not the causal reason for fever in the presence of a negative test result in children aged ≤5 years. Probability measure from 0 to 1. Abbreviations: NPV, negative predictive value; Sens, Sensitivity; Spec, Specificity.

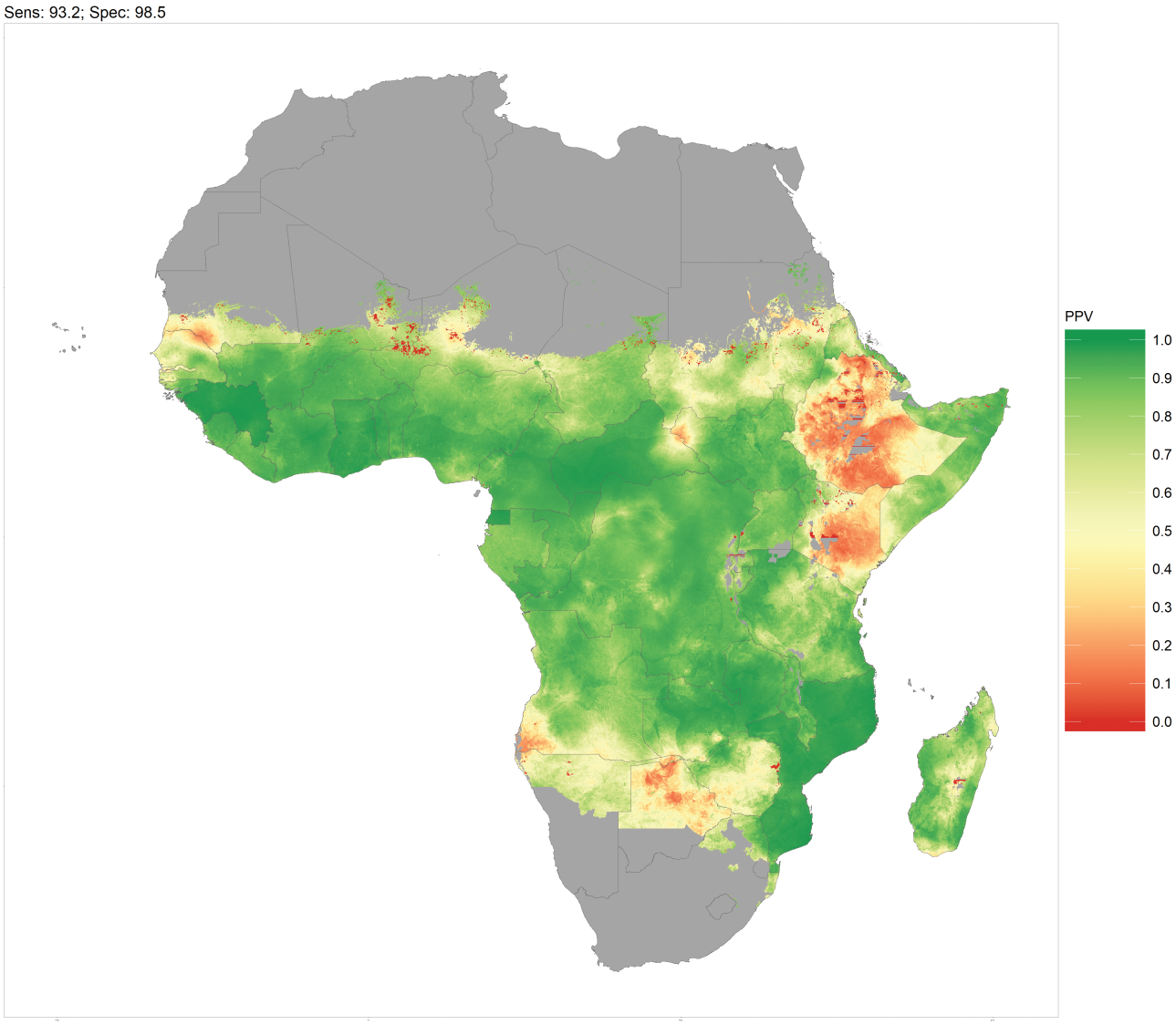

Figure 4. Parasite lactate dehydrogenase–based malaria rapid diagnostic tests. PPVs reflect the probability of malaria as the causal reason for fever in the presence of a positive test result in children aged ≤5 years. Probability measure from 0 to 1. Abbreviations: PPV, positive predictive value; Sens, Sensitivity; Spec, Specificity.

regions of Africa. This indicates that malaria is extremely unlikely to be a fever-causing factor in febrile children with a negative malaria RDT result and supports adherence to nonadministration of antimalarials by community health workers in the presence of a negative RDT. Instead, referral to higher levels of the healthcare sector is promoted where alternative fever causes can be assessed [5]. On the contrary, PPVs presented in this study highlight that a positive RDT result may not truly mirror malaria as the cause of fever in febrile children aged ≤5 years in virtually all evaluated countries of sub-Saharan Africa, globally the region of highest malaria case burden [5]. This implies that the administration of antimalarials alone may not constitute causal treatment, particularly in low-PPV settings. Thus, in low-PPV settings, it becomes increasingly important to investigate alternative causes of fever despite positive RDT results. Dedicated iCCM programs that aim to deliver simple and standardized management of childhood illnesses may need to reflect the overall low PPV to avoid misdiagnosis and withholding of appropriate medical management. Furthermore, algorithms should be best complemented by regional epidemiological data on nonmalaria-related causes of fever. Given the more favorable PPVs for pLDH-based RDTs than HRP2-based RDTs with NPVs being comparably high, usage of pLDH-based assays might be advocated in RDT-based test-and-treat approaches.

As a consequence of a changing malaria epidemiology and concurrent epidemics of newly emerging diseases, scenarios need to be envisioned that simulate changing MAF prevalences [5, 16, 17]. Furthermore, MAF prevalences might be subjected to seasonal variations.

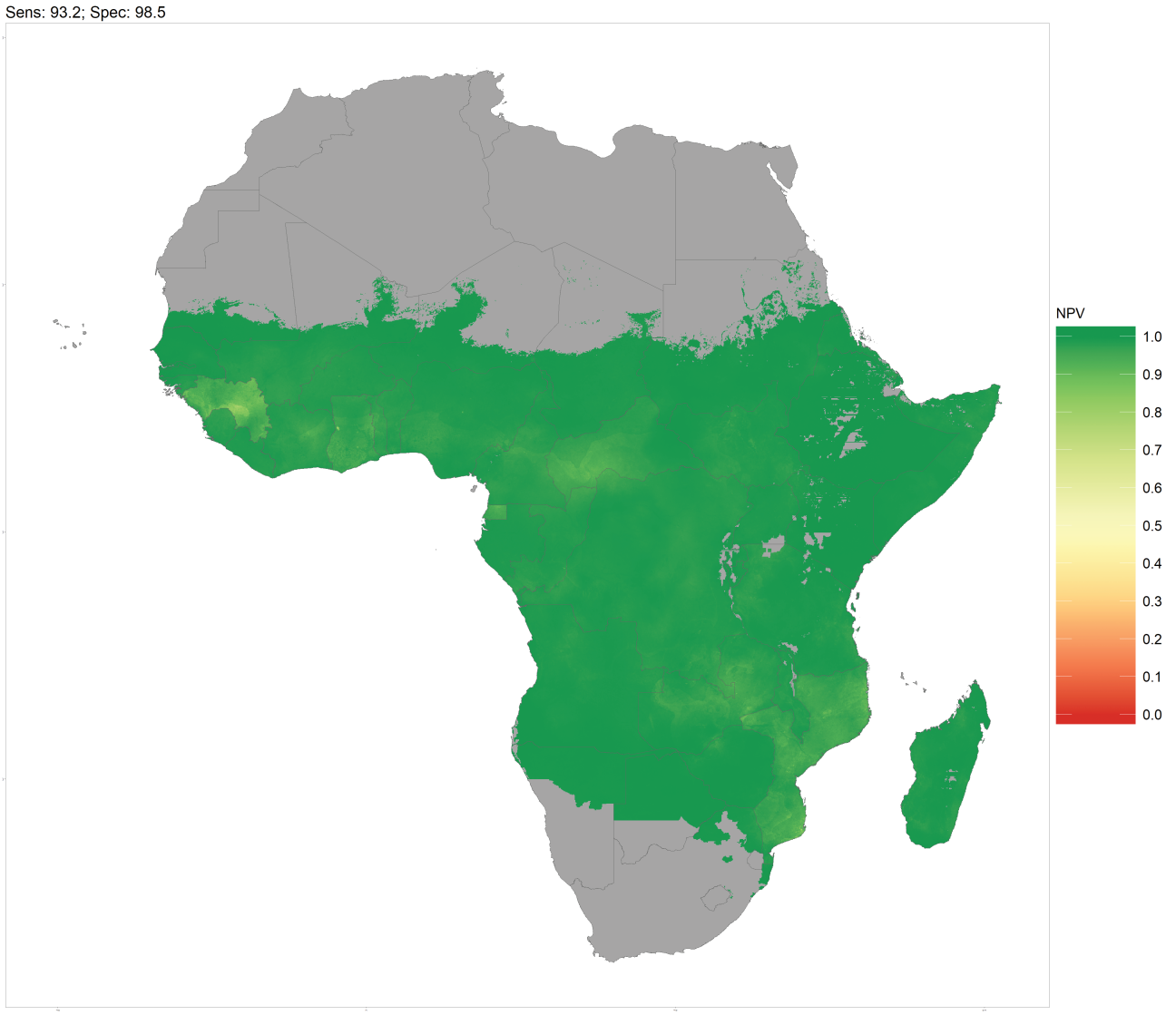

Figure 5. Parasite lactate dehydrogenase–based malaria rapid diagnostic tests. NPVs reflect the probability that malaria is not the causal reason for fever in the presence of a negative test result in children aged ≤5 years. Probability measure from 0 to 1. Abbreviations: NPV, negative predictive value; Sens, Sensitivity; Spec, Specificity.

Given constant values of sensitivity and specificity of an RDT, a falling MAF prevalence will decrease PPVs and thereby the validity of test-and-treat–based algorithms of iCCM programs. Such a scenario highlights the need for highly specific testing methods to corroborate malaria diagnosis. pLDH-based assays carry higher specificity than HRP2-based assays and may therefore be preferable. On the other hand, NPVs may become even more valid, as theory indicates rising NPVs in the wake of a falling prevalence (Supplementary Figures 1 and 2). Concordantly, the proportion of undertreated febrile children will decrease.

Given constant values of sensitivity and specificity, a rising MAF prevalence will increase PPVs and thereby the validity to which a positive RDT result reflects the causal reason for fever in a febrile child. On the other hand, a rising MAF prevalence will impair NPVs, thus potentially affecting the validity of negative test results. However, NPVs of an RDT with 95% sensitivity and specificity would only drop below 90% if prevalence increased to about 68% of the tested population (Supplementary Figures 1 and 2).

Next-generation RDTs have been described as being capable of detecting parasite blood densities that are about 10-fold lower than the lower limit of detection of conventional RDTs [18, 19]. Their role might be most important in large-scale malaria screening programs that aim to eliminate malaria from certain settings. However, it is not yet clear whether this new generation of RDT might contribute to improved case management of malaria-diseased individuals. A hospital-based study conducted in Ghana (n = 4169) that investigated the causes of pediatric febrile illnesses found that the frequency of gastrointestinal, lower

respiratory tract, and bloodstream infections became increasingly common as malaria parasite density decreased [12]. For malaria-endemic settings, this indicates that the causal factors of fever in hospitalized pediatric patients is often an infectious cause other than a concomitant ("nonfever-causing") malaria parasitemia. This holds particularly true for children and adolescents of an age with likely established semi-immunity against malaria [20]. In order to gain additional diagnostic information of causes of fever, the importance of exact quantification of malaria parasitemia by microscopy has been highlighted, as higher levels of parasitemia are more indicative of a symptomatic malaria episode [6, 12]. In that regard, the development of semiquantitative RDTs has been identified as a potential improvement for medical management. On the contrary, potential implementation of highly sensitive next-generation RDTs with a 10-fold lower limit of detection (ie, increased sensitivity) may counterintuitively lead to less favorable diagnostic performance when used in dedicated iCCM programs. Certainly, it would lead to more diagnoses of *Plasmodium* infections and thereby aid in malaria elimination efforts, however, not aiding to correctly identify causes of fever in febrile children.

HRP2 deletions have been described as the cause for some false-negative HRP2-based test results (ie, decreasing sensitivity of HRP2-based assays), and it is not clear how this might affect overall test performance in Africa in the future [21]. However, it might not greatly affect management of febrile children with positive test results, as PPVs are much more robust to drops in sensitivity than to drops in specificity. Theory indicates that NPVs are not significantly affected by decreases of assay sensitivity in the presence of low MAF prevalences (Supplementary Figure 2). However, unlike with overtreatment, the consequences of undertreatment are potentially lethal. Therefore, in case of large-scale spread of HRP2 deletions, RDTs with performance that is unaffected by HRP2 deletions (eg, pLDH-based) should be used.

RDT-detectable antigens can persist after successful treatment for a certain period, which can impair specificity of subsequent testing with RDTs [22]. Therefore, iCCM programs might potentially be able to increase the specificity of their testing algorithms by capturing any history of recent antimalarial treatment. However, diagnostic performance data used here stem from a meta-analysis that included numerous studies that also recruited participants with a history of recent malaria treatment; this suggests generalizability to individuals with recent a history of antimalarial treatment.

CONCLUSIONS

The prevalence of malaria-attributable fevers among febrile African children aged ≤5 years has decreased over the last decade, leading to a decline in the validity of positive RDT results represented by low PPVs for many African settings. Consequently, iCCM programs that administer antimalarial treatments to each febrile child with a positive malaria RDT may not provide causative treatment in the majority of febrile children in settings of low PPVs. On the contrary, NPVs were comparatively high, supporting the use of RDTs in community-based programs for decisions to withhold antimalarials in case of a negative RDT result. Africa-wide heat maps that depict predictive performance of RDTs hold important information for potential modification of algorithms for community health workers on fever management in settings of unfavorable PPV performance. Due to higher specificity, pLDH-based assays might be preferable to HRP2-based assays and lead to higher PPVs and a higher validity of test-and-treat algorithms in iCCM programs. Such algorithms should be complemented by information on other setting-specific major causes of fever.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. M. and M. R. had the idea for the research. J. M. and V. D. performed analyses for the project. V. D. visualized the data. All authors contributed to writing of the manuscript. All data used for this study are publicly accessible.

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References

1. World Health Organization. Malaria case management: operations manual. **2009**. Available at: https://www.who.int/malaria/publications/atoz/9789241598088/en/. Accessed 22 July 2020.
2. World Health Organization. Community-based reduction of malaria transmission. Consultation Report. **2012**. Available at: https://www.who.int/malaria/publications/atoz/9789241502719/en/. Accessed 22 July 2020.
3. World Health Organization. An equity-focused strategy to improve access to essential treatment services for children. **2012**. Available at: https://www.who.int/maternal_child_adolescent/documents/iccm_service_access/en/. Accessed 28 April 2020.
4. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. **2015**. Available at: https://www.who.int/malaria/publications/atoz/9789241549127/en/. Accessed 15 May 2020.
5. World Health Organization. World Malaria Report 2019. **2019**. Available at: https://www.who.int/publications-detail/world-malaria-report-2019. Accessed 15 May 2020.
6. Mischlinger J, Pitzinger P, Veletzky L, et al. Validity and reliability of methods to microscopically detect and quantify malaria parasitaemia. Trop Med Int Health **2018**; 23:980–91.
7. Murray CK, Gasser RA Jr, Magill AJ, Miller RS. Update on rapid diagnostic testing for malaria. Clin Microbiol Rev **2008**; 21:97–110.
8. Abba K, Deeks JJ, Olliaro P, et al. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. Cochrane Database Syst Rev **2011**;7:CD008122.
9. Altman DG, Bland JM. Diagnostic tests 2: predictive values. BMJ **1994**; 309:102.
10. Mischlinger J, Schernhammer E. A common trap of diagnostic tests : disease prevalence and positive predictive value. Wien Klin Wochenschr **2017**; 129:583–4.
11. Dalrymple U, Cameron E, Bhatt S, Weiss DJ, Gupta S, Gething PW. Quantifying the contribution of *Plasmodium falciparum* malaria to febrile illness amongst African children. Elife **2017**; 6.

12. Hogan B, Eibach D, Krumkamp R, et al.; Fever Without Source Study Group. Malaria coinfections in febrile pediatric Inpatients: a hospital-based study from Ghana. Clin Infect Dis **2018**; 66:1838–45.
13. Guerra CA, Hay SI, Lucioparedes LS, et al. Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. Malar J **2007**; 6:17.
14. Pfeffer DA, Lucas TCD, May D, et al. malariaAtlas: an R interface to global malariometric data hosted by the Malaria Atlas Project. Malar J **2018**; 17:352.
15. Mabey D, Vos T. Syndromic approaches to disease management. Lancet **1997**; 349:S26–8.
16. Kamorudeen RT, Adedokun KA, Olarinmoye AO. Ebola outbreak in West Africa, 2014-2016: epidemic timeline, differential diagnoses, determining factors, and lessons for future response. J Infect Public Health **2020**; 13:956–62.
17. Lone SA, Ahmad A. COVID-19 pandemic–an African perspective. Emerg Microbes Infect **2020**; 9:1300–8.
18. Slater HC, Ross A, Ouédraogo AL, et al. Assessing the impact of next-generation rapid diagnostic tests on *Plasmodium falciparum* malaria elimination strategies. Nature **2015**; 528:S94–101.
19. Pham NM, Karlen W, Beck HP, Delamarche E. Malaria and the "last" parasite: how can technology help? Malar J **2018**; 17:260.
20. Mischlinger J, Ronnberg C, Alvarez-Martinez MJ, et al. Imported malaria in countries where malaria is not endemic: a comparison of semi-immune and nonimmune travelers. Clin Microbiol Rev **2020**; 33:e00104–19.
21. Poti KE, Sullivan DJ, Dondorp AM, Woodrow CJ. HRP2: Transforming malaria diagnosis, but with caveats. Trends Parasitol **2020**; 36:112–26.
22. Foundation for Innovative New Diagnostics. How to use a rapid diagnostic test (RDT)—a guide for training at a village and clinic level. **2012**. Available at: https://www.finddx.org/wp-content/uploads/2016/03/paracheck_pf_manual_rev1_032612.pdf. Accessed 20 November 2020.