Prevalence of Malaria and Sexually Transmitted and Reproductive Tract Infections in Pregnancy in Sub-Saharan Africa

A Systematic Review

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Context Malaria and sexually transmitted infections/reproductive tract infections (STIs/RTIs) in pregnancy are direct and indirect causes of stillbirth, prematurity, low birth weight, and maternal and neonatal morbidity and mortality.

Objective To conduct a systematic review and meta-analysis of malaria and STI/RTI prevalence estimates among pregnant women attending antenatal care facilities in sub-Saharan Africa.

Data Sources PubMed, MEDLINE, EMBASE, the World Health Organization International Clinical Trials Registry, and reference lists were searched for studies reporting malaria, syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, or bacterial vaginosis among pregnant women attending antenatal care facilities in sub-Saharan Africa.

Study Selection Included studies were conducted in 1990-2011 with open enrollment. Studies from South Africa, where malaria is no longer endemic, were excluded.

Data Extraction Point prevalence estimates were corrected for diagnostic precision. A random-effects model meta-analysis was applied to produce pooled prevalence estimates.

Results A total of 171 studies met inclusion criteria, providing 307 point prevalence estimates for malaria or STIs/RTIs and including a total of 340 904 women. The pooled prevalence estimates (with 95% CIs and number of women with positive diagnosis) among studies in 1990-2011 in East and Southern Africa were as follows: syphilis, 4.5% (3.9%-5.1%; n=8346 positive diagnoses), *N gonorrhoeae*, 3.7% (2.8%-4.6%; n=626), *C trachomatis*, 6.9% (5.1%-8.6%; n=350), *T vaginalis*, 29.1% (20.9%-37.2%; n=5502), bacterial vaginosis, 50.8% (43.3%-58.4%; n=4280), peripheral malaria, 32.0% (25.9%-38.0%; n=11 688), and placental malaria, 25.8% (19.7%-31.9%; n=1388). West and Central Africa prevalence estimates were as follows: syphilis, 3.5% (1.8%-5.2%; n=851), *N gonorrhoeae*, 2.7% (1.7%-3.7%; n=73), *C trachomatis*, 6.1% (4.0%-8.3%; n=357), *T vaginalis*, 17.8% (12.4%-23.1%; n=822), bacterial vaginosis, 37.6% (18.0%-57.2%; n=1208), peripheral malaria, 38.2% (32.3%-44.1%; n=12 242), and placental malaria, 39.9% (34.2%-45.7%; n=4658).

Conclusion The dual prevalence of malaria and STIs/RTIs in pregnancy among women who attend antenatal care facilities in sub-Saharan Africa is considerable, with the combined prevalence of curable STIs/RTIs being equal to, if not greater than, malaria.

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There are 880 000 stillbirths[1] and 1.2 million neonatal deaths[2] each year in sub-Saharan Africa. Low birth weight (<2.5 kg), attributable to intrauterine growth retardation, preterm delivery, or both, is the leading risk factor for neonatal mortality.[3] Intrauterine infection is implicated in stillbirth[4] and is associated with 25% to 40% of preterm births.[5] Sexually transmitted infections and reproductive tract infections (STIs/RTIs)[6] and malaria[7] are associated with adverse birth outcomes, but both may be mitigated with preventive or presumptive treatment or by repeated screening and treatment throughout the antenatal period. The extent to which either approach may be beneficial depends on the underlying prevalence of STIs/RTIs and malaria in pregnancy. This systematic review and meta-analysis provide estimates for the dual prevalence of STIs/RTIs and malaria in pregnancy among women attending antenatal care facilities in sub-Saharan Africa.

METHODS

We searched 3 databases, PubMed, MEDLINE, and EMBASE, in November 2011 using Medical Subject Headings and free text terms, respectively; the World Health Organization (WHO) International Clinical Trials Registry; and relevant reference lists to identify studies conducted between 1990-

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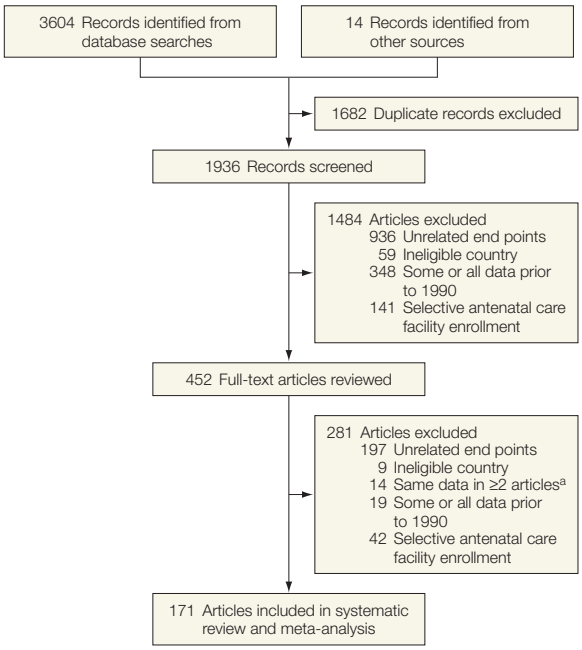
Figure 1. Identification, Screening, and Eligibility of Studies in the Meta-analysis



[a] Data believed to have appeared in more than 1 article were reviewed in full text and therefore do not appear under records excluded.

2011 that reported point prevalence estimates for STIs/RTIs, malaria, or both among pregnant women attending antenatal care facilities in sub-Saharan Africa (eAppendix 1; available at http://www.jama.com). If 2 or more prevalence estimates were reported—whether the result of a comparative diagnostic study, use of the same diagnostic method on multiple occasions, or subsequent use of a more sensitive assay—we used the higher/highest measurement in our analysis.

Our aim was to establish the dual prevalence of these infections in pregnancy among women receiving antenatal care without inflating estimates by including studies that selectively enrolled women from high-risk groups. Thus, studies that enrolled subsets of women from the antenatal care population were excluded (eg, only pregnant women with human immunodeficiency virus [HIV]). Studies of commercial sex workers, women seeking treatment at STI facilities or family planning facilities, or nonpregnant women tested in community-based surveys were also excluded. Multiyear studies that included pre-1990 data were excluded, as were studies from South Africa, where malaria is no longer endemic.

Records retrieved were all in English, although several abstracts had been translated from Chinese, Danish, Dutch, French, German, Italian, Portuguese, and Swedish. One author (R.M.C.) conducted the data retrieval. Data abstraction was not blinded to author or publication but was performed independently and in duplicate by R.M.C. and a research assistant, reviewing records against inclusion/exclusion criteria to identify 3618 records of interest. Any discrepancies were resolved by D.C. Two authors (P.M. and D.M.) and another researcher assisted R.M.C. in the identification and classification of STI/RTI diagnostic methods; D.C. did the same with R.M.C. for malaria studies. No evidence of publication bias was found using funnel-plot assessment as described by Sterne et al.[8] Given that data for this review have been drawn from studies reporting point prevalence estimates without intervention, the potential for publication bias should be minimal.

Point prevalences and 95% confidence intervals were calculated for each study. We then applied a standard method[9] for correcting errors of magnitude with the known sensitivity and specificity of individual assays (eAppendix 2 and eAppendix 3) to increase the precision of each point prevalence estimate. Corrected point prevalence data were then used to generate pooled prevalence estimates and corresponding 95% confidence intervals. We stratified results by subregion (East and Southern Africa vs West and Central Africa) because of underlying differences in epidemiology, particularly the extent to which HIV modulates the transmission of malaria and STIs/RTIs.

We conducted the meta-analysis with random-effects models,[10] accounting for the possibility of heterogeneity between studies, and assessed our results with the Q statistic. Separate sensitivity analyses were performed for studies conducted before and after the year 2000 to examine temporal changes in prevalence. Using Stata/IC version 12 software[11] to generate the random-effects meta-analysis model, we produced forest plots to display the point prevalence and 95% confidence intervals of individual studies as well as the pooled estimates and 95% confidence intervals for all strata.

RESULTS

A total of 171 studies met inclusion criteria, providing 307 point prevalence estimates and including a total of 340 904 women. Search results are summarized in FIGURE 1. The TABLE summarizes the pooled mean prevalence estimates of 1990-2011 with subanalyses for 1990-1999 and 2000-2011. Results for the period 1990-2011 are presented in FIGURE 2, plotted by subregion along with the lowest and highest point estimates reported. Detailed analyses by infection type and subregion are available online (eTable 1 and eFigure 1 [syphilis], eTable 2 and eFigure 2

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Table. Pooled Mean Prevalence Estimates Among Pregnant Women Attending Antenatal Care Facilities in Sub-Saharan Africa

Infection by Subregion	Pooled Mean Prevalence, % (95% CI)[a]	No. of Women: Positive	No. of Women: Tested	No. of Women: Median No. With Positive Diagnosis	Study Sample Size, Range	No. of Countries	No. of Studies	ANC Facilities per Study, Range	Heterogeneity, %
1990-2011									
East and Southern Africa									
Syphilis	4.5 (3.9 to 5.1)	8346	136 686	54	85-52 405	11	41	1-57	[c]
N gonorrhoeae	3.7 (2.8 to 4.6)	626	17 220	20	145-9104	7	14	1-13	87.5
C trachomatis	6.9 (5.1 to 8.6)	350	5159	34	151-964	8	10	1-13	85.9
T vaginalis	29.1 (20.9 to 37.2)	5502	28 189	86	100-9137	9	18	1-13	[c]
Bacterial vaginosis	50.8 (43.3 to 58.4)	4280	14 112	245	100-3046	8	11	1-13	[c]
Peripheral parasitemia	32.0 (25.9 to 38.0)	11 688	47 443	195	86-5093	8	35	1-10	[c]
Placental parasitemia	25.8 (19.7 to 31.9)	1388	6649	86	85-2502	7	12	1-9	[c]
West and Central Africa									
Syphilis	3.5 (1.8 to 5.2)	851	10 797	18	205-4100	9	11	1-98	[c]
N gonorrhoeae	2.7 (1.7 to 3.7)	73	2737	17	230-1160	8	5	1-4	67.2
C trachomatis	6.1 (4.0 to 8.3)	357	5414	35	261-1160	8	10	1-4	94.7
T vaginalis	17.8 (12.4 to 23.1)	822	9806	57	86-2657	7	12	1-4	[c]
Bacterial vaginosis	37.6 (18.0 to 57.2)	1208	7435	138	350-2657	6	7	1-3	[c]
Peripheral parasitemia	38.2 (32.3 to 44.1)	12 242	43 312	127	26-6370	10	56	1-55	[c]
Placental parasitemia	39.9 (34.2 to 45.7)	4658	27 535	168	36-8310	8	23	1-6	[c]
1990-1999									
East and Southern Africa									
Syphilis	6.1 (5.0 to 7.2)	6168	97 055	79	85-52 405	8	21	1-23	[c]
N gonorrhoeae	3.7 (2.7 to 4.6)	547	15 446	18	151-9104	6	9	1-12	82.5
C trachomatis	9.4 (6.0 to 12.7)	194	2395	36	151-964	4	5	1-12	88.2
T vaginalis	32.8 (18.6 to 47.1)	4314	17 710	74	100-9137	5	10	1-12	[c]
Bacterial vaginosis	51.5 (35.5 to 67.5)	1876	7039	109	100-3046	5	6	1-1	[c]
Peripheral parasitemia	34.9 (25.1 to 44.7)	7563	29 068	327	102-5093	7	16	1-10	[c]
Placental parasitemia	25.2 (16.0 to 34.3)	588	3271	124	232-2502	3	3	1	[c]
West and Central Africa									
Syphilis	3.8 (1.5 to 6.2)	773	7106	13	205-4100	6	17	1-4	[c]
N gonorrhoeae	3.0 (1.8 to 4.2)	70	2507	18	350-1160	7	4	1-4	67.2
C trachomatis	7.5 (4.6 to 10.0)	339	4632	44	350-1160	7	5	1-4	94.7
T vaginalis	23.5 (15.6 to 31.5)	721	4585	73	86-1160	6	8	1-4	[c]
Bacterial vaginosis	46.0 (24.2 to 67.8)	640	2645	132	350-646	5	5	1-3	[c]
Peripheral parasitemia	43.4 (34.1 to 52.7)	5543	16 671	178	26-2104	7	19	1-17	[c]
Placental parasitemia	42.6 (34.9 to 50.3)	2445	19 582	233	64-8310	6	9	1-2	[c]
2000-2011									
East and Southern Africa									
Syphilis	2.9 (2.1 to 3.6)	2178	39 631	32	245-17 277	8	17	1-57	[c]
N gonorrhoeae	4.9 (1.8 to 7.9)	79	1774	21	145-835	6	4	1-13	91.9
C trachomatis	5.2 (3.4 to 7.1)	156	2764	25	151-835	6	5	1-13	79.6
T vaginalis	24.9 (18.3 to 31.5)	1188	10 479	98	151-2917	8	8	1-13	[c]
Bacterial vaginosis	50.3 (43.9 to 56.7)	2404	7073	253	247-2555	6	5	1-13	[c]
Peripheral parasitemia	29.5 (22.4 to 36.5)	4125	18 375	157	86-2459	8	19	1-9	[c]
Placental parasitemia	26.5 (16.7 to 36.4)	800	3378	58	85-726	3	9	1-9	[c]
West and Central Africa									
Syphilis	2.5 (0.4 to 4.6)	78	3691	21	230-2133	4	5	1-98	88.6
N gonorrhoeae	1.6 (0.0 to 3.3)	3	230	3	230	3	1	1-1	NA[b]
C trachomatis	1.9 (0.2 to 3.5)	18	782	9	261-521	2	2	1-2	55.8
T vaginalis	4.5 (2.5 to 6.6)	101	5221	25	201-2657	2	4	1-4	92.7
Bacterial vaginosis	16.7 (−12.6 to 46.1)	604	4790	302	2133-2657	2	2	1-2	[c]
Peripheral parasitemia	35.1 (28.2 to 41.9)	6699	26 641	97	38-6370	8	36	1-55	[c]
Placental parasitemia	38.0 (28.4 to 47.6)	2213	7953	84	36-1875	6	15	1-6	[c]

Abbreviation: ANC, antenatal care; *C trachomatis*, *Chlamydia trachomatis*; *N gonorrhoeae*, *Neisseria gonorrhoeae*; *T vaginalis*, *Trichomonas vaginalis*.

[a] Note that dividing total No. of positive diagnoses by total No. of tested women does not account for diagnostic errors. A standard method[9] of correcting errors of known magnitude has been applied to these data based on the sensitivity and specificity of individual diagnostic tests. Uncorrected and corrected point estimates from each study are presented in the eTables.

[b] Not applicable (NA) because there is only 1 study.

[c] Heterogeneity greater than 97.0%.

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[*Neisseria gonorrhoeae*], eTable 3 and eFigure 3 [*Chlamydia trachomatis*], eTable 4 and eFigure 4 [*Trichomonas vaginalis*], eTable 5 and eFigure 5 [bacterial vaginosis], eTable 6 and eFigure 6 [peripheral malaria], and eTable 7 and eFigure 7 [placental malaria]), with key findings reported herein. In all instances, prevalence estimates have been corrected to account for diagnostic errors as previously described.

Syphilis

The pooled mean prevalence of syphilis in East and Southern Africa was 4.5% (95% CI, 3.9%-5.1%), with the highest estimate, 13.7% (95% CI, 9.0%-18.5%), in Vilanculos, Mozambique, based on rapid plasma reagin (RPR) testing and *Treponema pallidum* hemagglutination confirmation.[12] In West and Central Africa, the pooled mean prevalence of serological syphilis was 3.5% (95% CI, 1.8%-5.2%). Yaoundé, Cameroon, reported the highest point estimate of 16.3% (95% CI, 15.2%-17.4%) using a *T pallidum* hemagglutination assay that confirms syphilis infection, although not necessarily active cases.[13]

Neisseria gonorrhoeae

In East and Southern Africa, the pooled prevalence was 3.7% (95% CI, 2.8%-4.6%), with the highest point estimate of 23.3% (95% CI, 16.4%-30.2%) observed in Manhiça, Mozambique.[12] The pooled mean prevalence of *N gonorrhoeae* in West and Central Africa was 2.7% (95% CI, 1.7%-3.7%); the highest individual estimate, 4.6% (95% CI, 2.8%-6.3%), came from a study in Abidjan, Côte d'Ivoire, that used culture diagnostic methods.[14]

Chlamydia trachomatis

The pooled prevalence of *C trachomatis* infection in East and Southern Africa was 6.9% (95% CI, 5.1%-8.6%), with Khartoum, Sudan, reporting the highest prevalence estimate of 23.2% (95% CI, 16.5%-29.9%) as detected by an enzyme immunoassay.[15] In West and Central Africa, the pooled mean prevalence was 6.1% (95% CI, 4.0%-8.3%). The highest prevalence, 16.4% (95% CI, 12.6%-20.1%) based on culture or enzyme immunoassay, was observed in Pikine, Senegal.[16]

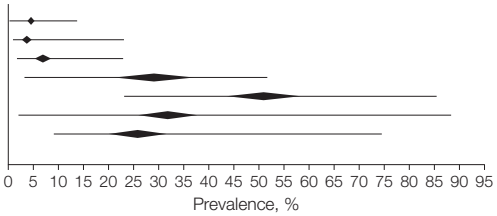
Trichomonas vaginalis

The pooled prevalence of *T vaginalis* infection was 29.1% (95% CI, 20.9%-37.2%) among women in East and Southern Africa, compared with 17.8% (95% CI, 12.4%-23.1%) in West and Central Africa. The highest point estimate in East and Southern Africa was 51.7% (95% CI, 41.9%-61.5%), reported in a refugee camp of Rwandans in Tanzania,[17] as diagnosed by wet-mount microscopy. The highest prevalence estimate in West and Central Africa, 52.0% (95% CI, 47.6%-56.4%), was in Jos, Nigeria, where *T vaginalis* was identified by the same method.[18]

Figure 2. Curable STI/RTI and Malaria Infection Among Pregnant Women Attending Antenatal Facilities in Africa by Subregion

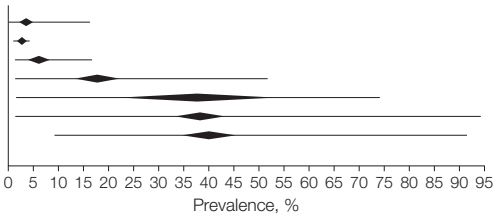
East and Southern Africa

Infection	No. of Women: Positive Diagnosis	No. of Women: Tested	Pooled Prevalence Estimates, % (95% CI)	Lowest to Highest Point Estimates, Range, %
Syphilis	8346	136 686	4.50 (3.90-5.10)	0.10-13.70
Neisseria gonorrhoeae	626	17 220	3.70 (2.80-4.60)	1.40-23.30
Chlamydia trachomatis	350	5159	6.90 (5.10-8.60)	2.00-23.20
Trichomonas vaginalis	5502	28 189	29.10 (21.00-37.20)	3.90-51.70
Bacterial vaginosis	4280	14 112	50.80 (43.30-58.40)	23.50-85.50
Peripheral malaria	11 688	47 443	32.00 (25.90-38.00)	2.10-87.90
Placental malaria[a]	1388	6649	25.80 (19.70-31.90)	8.50-74.70



West and Central Africa

Infection	No. of Women: Positive Diagnosis	No. of Women: Tested	Pooled Prevalence Estimates, % (95% CI)	Lowest to Highest Point Estimates, Range, %
Syphilis	851	10 797	3.50 (1.80-5.20)	0.10-16.30
Neisseria gonorrhoeae	73	2737	2.70 (1.70-3.70)	1.60-4.60
Chlamydia trachomatis	357	5414	6.10 (4.00-8.30)	1.40-16.40
Trichomonas vaginalis	822	9806	17.80 (12.40-23.10)	1.60-52.00
Bacterial vaginosis	1208	7435	37.60 (18.00-57.20)	18.00-74.50
Peripheral malaria	12 242	43 312	38.20 (37.30-44.10)	0.90-94.50
Placental malaria[a]	4658	27 535	39.90 (34.20-45.70)	9.00-91.60



Diamonds indicate pooled mean prevalence estimates; the extremes of the diamonds indicate 95% CIs. Horizontal bars indicate lowest to highest point prevalence estimates. STI/RTI indicates sexually transmitted infection/reproductive tract infection.
[a] Placental malaria is measured at delivery.

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Bacterial Vaginosis

The burden of bacterial vaginosis was higher than any other STI/RTI in both subregions. In East and Southern Africa, the pooled prevalence estimate was 50.8% (95% CI, 43.4%-58.4%). The highest point estimate was 85.5% (95% CI, 82.8%-88.1%) in Blantyre, Malawi, where Amsel criteria were used for diagnosis.[17] In West and Central Africa, the pooled prevalence estimate was 37.6% (95% CI, 18.0%-57.2%), with the highest point estimate at 74.5% (95% CI, 70.0%-79.1%) in Praia, Cape Verde, based on clue cell count.[19]

Malaria

Peripheral Malaria. The pooled prevalence of peripheral malaria in East and Southern Africa was 32.0% (95% CI, 25.9%-38.0%). The highest subregional prevalence, 87.9% (95% CI, 85.7%-90.1%), was reported from Hoima, Uganda, where diagnosis was made by microscopy.[20] In West and Central Africa, the pooled prevalence of peripheral malaria parasitemia was 38.2% (95% CI, 32.3%-44.1%). The highest point estimate was 94.9% (95% CI, 88.0%-102.0%) in Ngali II, Cameroon, as identified by polymerase chain reaction (PCR) diagnosis.[21]

Placental Malaria. For placental malaria, measurable only after delivery, the pooled prevalence in East and Southern Africa was 25.8% (95% CI, 19.7%-31.9%); the highest point estimate, 74.7% (95% CI, 65.5%-84.0%), was based on histological diagnosis in Kisumu, Kenya.[22] In West and Central Africa, the pooled prevalence was 39.9% (95% CI, 34.2%-45.7%), and the highest point prevalence was 91.6% (95% CI, 84.8%-94.4%) as diagnosed by placental histology, impression, and smears with microscopy in Ebolowa, Cameroon.[23]

Dual Prevalence of STIs/RTIs and Malaria

Only 5 publications reported the prevalence of syphilis and malaria,[24-28] and no single article reported coinfection of malaria and STIs/RTIs. Subanalysis in a prospective cohort study of pregnant women in Tanzania provided some of the only published data on coinfection: 48.3% of RPR-positive women also had placental parasitemia and 35.0% of RPR-negative women had malaria-infected placentas ($P < .001$).[29]

COMMENT

This systematic review of STIs/RTIs and malaria prevalence estimates over a 20-year period suggests that a considerable burden of malaria and STIs/RTIs exists at the population level among pregnant women attending antenatal facilities in sub-Saharan Africa. However, the absence of reports on coinfection makes it impossible to describe the prevalence of malaria only, curable STIs/RTIs only, or coinfection in pregnancy.

The GRADE approach to data quality assessment[30] was considered inappropriate for this particular meta-analysis. It is a useful and transparent tool for the analysis of treatment outcomes following contrasting interventions produced by different study designs. However, because we included studies that had open enrollment in the antenatal care setting and we were not investigating the effect of medical intervention, we did not expect the population prevalence of STIs/RTIs and malaria in pregnancy to vary across study designs. In addition, the GRADE system requires ranking of evidence by outcomes of interest, scored as high, intermediate, low, or very low. In this review, we could have assigned quality scores to point prevalence estimates, but that would have introduced a limited but unavoidable level of subjectivity. Thus, we chose instead to improve the precision of each point estimate with a standard method[9] for correcting errors of known magnitude before incorporating data into the random-effects models. This same approach has been used with prevalence data from Tanzania to compare STI/RTI estimates derived by disparate diagnostic tests.[31] We present corrected and uncorrected point prevalence estimates by study in eTable 1 through eTable 7.

Diagnostic methods and tools have changed for many pathogens during the period covered in this review. The advent of molecular tests such as PCR and ligase chain reaction has allowed researchers in recent years to detect infection where older diagnostic methods may have failed to do so. Although our statistical correction for diagnostic errors can make data more comparable, the pooled mean prevalence of STIs/RTIs and malaria is still probably an underestimate of the true burden of disease. Among 59 studies providing estimates for syphilis prevalence, 45 used the nontreponemal RPR or venereal disease research laboratory tests confirmed by a *Treponema*-specific test, reflecting wide acceptance of the diagnostic gold standard. Because biological false-positive nontreponemal test results can be produced by malaria and other infections, the burden of syphilis in studies that did not use treponemal confirmatory testing may be overstated.

A variety of diagnostic methods were used for identifying *N gonorrhoeae* and *C trachomatis* infections, whereas wet-mount microscopy was used in all but 2 studies reporting trichomoniasis prevalence, a method notoriously lacking sensitivity compared with culture or molecular tests.[32,33] Bacterial vaginosis was diagnosed using 4 methods: Nugent score, Spiegel criteria, Amsel criteria, and clue cell prevalence estimates. The Nugent score[34] is the preferred objective method and was used in studies reporting the 7 highest rates of infection from East and Southern Africa. Thus, the pooled mean prevalence would likely have been higher had the Nugent score been used in all studies.

Peripheral parasitemia may be underrepresented for 2 reasons. Infection tends to be highest between gestational weeks 9 through 16, declining until term.[35,36] No studies appeared to have measured peripheral parasitemia during this peak period. Another important source of underestimated disease burden is that most malaria diagnoses were based on microscopy without molecular test correction. A study in Blantyre, Malawi, illustrates the extent to which underdiagnosis may occur with conventional microscopy; the

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prevalence of peripheral parasitemia of 51.9% (95% CI, 43.4%-60.3%) was found by PCR, while microscopy detected infection only in 14.9% (95% CI, 11.8%-18.0%) of pregnant women.[37]

The dual prevalence of STIs/RTIs and malaria varied in the subregions we analyzed. Overall, East and Southern Africa has a greater burden of STIs/RTIs compared with West and Central Africa. Several factors that are linked to exposure may contribute to this difference, including higher prevalence of STIs/RTIs circulating at the community level, patterns of male circumcision as well as sexual behavior related to age of sexual debut, age at first marriage, premarital sex, and number of total partners and concurrent sex partners. The prevalence of HIV, for example, remains substantially higher in East and Southern Africa compared with the West and Central subregion. According to the Joint United Nations Programme on HIV/AIDS, 34% of the world's HIV-positive population was living in 10 countries of Southern Africa in 2010.[38] The epidemic in East Africa has declined over the past decade, but HIV prevalence remains higher than in West and Central Africa.

Peripheral and placental malaria is slightly higher in West and Central Africa compared with the East and Southern subregion. This may be due to greater seasonal variation in transmission within West and Central Africa. Recent declines in malaria transmission within selected locales of Africa will likely translate into fewer pregnant women acquiring immunity from one pregnancy to the next. Thus, all women in their reproductive years (rather than just those in their first or second pregnancies) may remain vulnerable to malaria in the years ahead until the absolute risk of exposure is negligible.

Human immunodeficiency virus and malaria interact to increase parasitic infection of the placenta and incidence of low birth weight.[39] *Plasmodium falciparum* infection also increases viral load among HIV-positive pregnancy women.[40] New evidence suggests that malaria parasites are more likely to develop wild-type mutations following exposure to sulfadoxine-pyrimethamine as intermittent preventive treatment during pregnancy (IPTp) when administered to HIV-positive women.[41] The interaction between STIs/RTIs and HIV has been well established, although providing presumptive treatment for STIs/RTIs to pregnant women in Rakai, Uganda, has not shown protective effect against maternal to child transmission of HIV.[42] However, malaria chemoprophylaxis was not provided in this study; therefore, the potential modulating effect of malaria on maternal to child transmission in the presence of STIs/RTIs remains unknown.

Our study has several limitations. An unavoidable but important limitation is the inherent delay between gathering evidence at the clinic level and public dissemination. This is important in our study because HIV prevention campaigns, including STI/RTI screening and treatment programs, have made inroads in reducing transmission in many settings. To capture these reductions with greater precision, more recent data are needed. Another limitation is that even after stratifying by geography and age of study, heterogeneity among studies persisted. The random-effects models, in turn, produced wide 95% confidence intervals in some instances. In addition, because we relied on evidence from English-language sources and abstracts that had been translated into English, we may have identified fewer studies from researchers who publish in other languages.

There is a major risk of adverse birth outcomes associated with malaria and STIs/RTIs in pregnancy. More than 30 million pregnant women are at risk of infection each year in sub-Saharan Africa.[43] Malaria is associated with intrauterine growth retardation, preterm delivery, low birth weight,[44,45] stillbirth,[44] early neonatal death,[44] and maternal anemia.[45] In Tanzania, *T pallidum* is associated with 51% of stillbirths and 24% of preterm live births.[46] *Neisseria gonorrhoeae* is associated with a 2-fold increase in the risk of preterm delivery,[47] whereas the risk of early preterm delivery in the presence of *C trachomatis* infection is 4 times higher.[48] Untreated *C trachomatis* infects the eyes of 50% of newborns at delivery, and pneumonia will develop in 10% to 20% of these infants.[49,50] *Neisseria gonorrhoeae* and *C trachomatis* are common causes of ophthalmia neonatorum and may lead to corneal scarring and blindness if untreated. *Trichomonas vaginalis* infection is associated with a 2-fold increase in preterm delivery,[51] as is bacterial vaginosis, the odds of which are 7 times higher when the condition manifests prior to 16 weeks' gestation.[52] Bacterial vaginosis is also significantly associated with the risk of spontaneous abortion.[52] Within this context, progress toward the maternal and child health targets of Millennium Development Goals may be possible by improving malaria and STI/RTI control measures within the antenatal care package.

Several current infection control strategies are included in the antenatal care package. In areas of stable malaria transmission, WHO recommends that pregnant women sleep under insecticide-treated mosquito bed nets and receive 2 to 3 treatment courses of SP-IPTp during antenatal consultations. Drug resistance to SP has compromised the protective effect of SP-IPTp in recent years, prompting a need to identify efficacious drugs and new strategies to prevent malaria in pregnancy.[53]

WHO recommends syphilis screening and treatment for pregnant women at their first antenatal visit. For other curable STIs/RTIs, WHO suggests using syndrome-based algorithms to guide diagnosis and treatment. However, the vast majority of gonococcal (80%) and chlamydial (70%-75%) infections in women are asymptomatic[54] and therefore never diagnosed. Consequently, the algorithm based on vaginal discharge syndrome has a low sensitivity (30%-80%) and specificity (40%-80%) for *N gonorrhoeae* and *C trachomatis* among pregnant women.[55-57] Syndromic management has slightly higher sensitivity for *T vaginalis* (54%-83%) and bacterial vaginosis (51%-69%), with moderate specificity (40%-54% for *T vaginalis* and 40%-58% for bacterial vaginosis).[58]

In addition, potential new directions for the antenatal care package have been

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suggested, including use of novel drugs and rapid diagnostic tests. Several trials of azithromycin-based combination therapies are under investigation for use in IPTp. Azithromycin has modest antimalarial properties but needs a partner antimalarial drug against *P falciparum*.[59] Despite concerns about drug resistance,[60] a 2-g dose of azithromycin has resulted in cure rates of 97.7% (95% CI, 94.0%-99.4%) of syphilis cases in a study in Tanzania.[61] A single 2-g dose of azithromycin was 98.9% (95% CI, 97.9%-100%) efficacious against *N gonorrhoeae* in the United States,[62] while meta-analysis showed that 1 g cures 96.5% (95% CI, 95.3%-97.7%) of *C trachomatis* infections.[63] A trial in Malawi using 1 g of azithromycin administered twice with SP-IPTp reduced the risk of *T vaginalis* 35% ($P=.02$).[64] Azithromycin-based combinations could protect against bacterial vaginosis if administered early in pregnancy; a meta-analysis of antibiotic therapy for the treatment of bacterial vaginosis in pregnancy prior to gestational week 20 is associated with a significant reduction in the risk of preterm birth.[65]

Novel use of rapid diagnostic tests may replace IPTp with sulfadoxine-pyrimethamine altogether if used for intermittent screening and treatment for malaria during antenatal visits. Intermittent screening and treatment with artesunate-amodiaquine was noninferior to IPTp with sulfadoxine-pyrimethamine in Ghana in an area where sulfadoxine-pyrimethamine resistance was low; the incidence of low birth weight was similar between the IPTp with sulfadoxine-pyrimethamine and intermittent screening and treatment groups among multigravid mothers (11.3% vs 11.3%) and among primigravid mothers (16.1% vs 17.2%).[66] Rapid point-of-care tests for HIV have revolutionized the uptake and performance of voluntary counseling and testing[67] and are used in some antenatal settings in Africa. Point-of-care tests for syphilis are increasingly available, making possible same-day results and prompt treatment.[68,69]

Mitigating the dual prevalence of malaria and STIs/RTIs will require improvements in the Safe Motherhood package.[70] Bacterial vaginosis requires particular attention given its high prevalence. Clinical trials are needed to investigate the protective effect of presumptive treatment of bacterial vaginosis with metronidazole at time points that are biologically optimal and operationally feasible. It is less clear whether pregnancy outcomes would be improved more with point-of-care tests and treatment for HIV, syphilis, and malaria, while syndromic management is provided for the remaining curable STIs/RTIs—or if maternal, fetal, and newborn health will be better if women are given point-of-care tests for HIV and syphilis along with azithromycin-based combination therapy in IPTp. Rigorously conducted clinical trials are urgently needed.

CONCLUSION

The dual prevalence of malaria and STIs/RTIs is evident among pregnant women who attend antenatal facilities in sub-Saharan Africa. As malaria control and elimination efforts are brought to scale, the relative contribution of STIs/RTIs to adverse birth outcomes most likely will increase proportionately. Coinfection prevalence estimates for malaria and STIs/RTIs need to be established and routinely reported. Rigorous studies using molecular diagnostic methods are needed to characterize more accurately the prevalence of these infections and their clinical consequences. Clinical trials are needed to compare birth outcomes, operational feasibility/acceptability, and cost-effectiveness of IPTp with azithromycin-based combination therapy against an approach of integrated screening and treatment for malaria and STIs/RTIs.

Author Contributions: Mr Chico and Dr Chandramohan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chandramohan.
Acquisition of data: Chico.
Analysis and interpretation of data: Chico, Mayaud, Mabey, Ariti, Ronsmans, Chandramohan.
Drafting of the manuscript: Chico.
Critical revision of the manuscript for important intellectual content: Chico, Mayaud, Mabey, Ariti, Ronsmans, Chandramohan.
Statistical analysis: Chico, Ariti.
Administrative, technical, or material support: Chico, Mayaud, Mabey, Ariti, Ronsmans, Chandramohan.
Study supervision: Chandramohan.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Chico reports having previously received funding as part of 2 studies co-financed by Pfizer and the Medicines for Malaria Venture that are investigating the use of azithromycin plus chloroquine in IPTp. No other disclosures were reported.
Online-Only Material: eAppendixes 1 through 3, eTables 1 through 7, and eFigures 1 through 7 are available at http://www.jama.com.
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