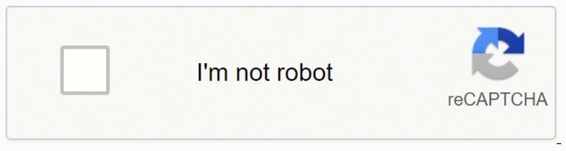
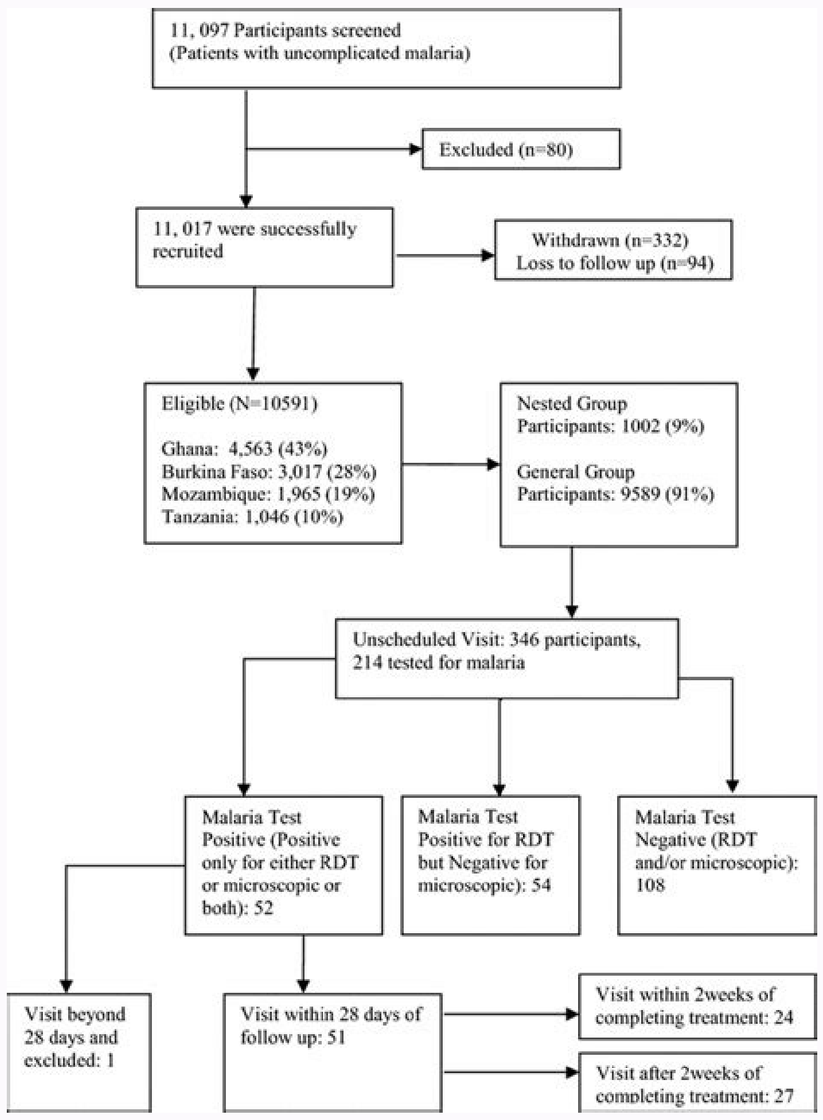


Open

Malaria iap guidelines



Am. J. Trop. Med. Hyg., 90(1), 2014, pp. 20–32
doi:10.4269/ajtmh.13-0019

Hospitalizations and Costs Incurred at the Facility Level after Scale-up of Malaria Control: Pre-Post Comparisons from Two Hospitals in Zambia

Alison B. Comfort,* Janneke H. van Dijk, Sungano Mharakurwa, Kathryn Stillman, Rose Gabert, Sonali Korde, Nancy Nachbar, Yann Derriennic, Stephen Musau, Petan Hamazakaza, Khozya D. Zyambo, Nancy M. Zyongwe, Busiku Hamainza, and Philip E. Thuma

Abt Associates, Cambridge, Massachusetts; Clinical Research Department, Macha Research Trust, Choma, Zambia; Johns Hopkins Malaria Research Institute, Malaria Research Department, Macha Research Trust, Choma, Zambia; Abt Associates, Bethesda, Maryland; President's Malaria Initiative, Bureau of Global Health, United States Agency of International Development, Washington, District of Columbia; Farming Systems and Social Sciences, Zambia Agricultural Research Institute, Kabwe, Zambia; Department of Paediatric and Child Health, Livingstone General Hospital, Livingstone, Zambia; Southern Province Medical Office, Zambia Integrated Systems Strengthening Programme, Abt Associates, Livingstone, Zambia; National Malaria Control Center, Lusaka, Zambia

Abstract. There is little evidence on the impact of malaria control on the health system, particularly at the facility level. Using retrospective, longitudinal facility-level and patient record data from two hospitals in Zambia, we report a pre-post comparison of hospital admissions and outpatient visits for malaria and estimated costs incurred for malaria admissions before and after malaria control scale-up. The results show a substantial reduction in inpatient admissions and outpatient visits for malaria at both hospitals after the scale-up, and malaria cases accounted for a smaller proportion of total hospital visits over time. Hospital spending on malaria admissions also decreased. In one hospital, malaria accounted for 11% of total hospital spending before large-scale malaria control compared with < 1% after malaria control. The findings demonstrate that facility-level resources are freed up as malaria is controlled, potentially making these resources available for other diseases and conditions.

INTRODUCTION

According to the most recent estimates from the World Health Organization World Malaria Report 2012, malaria accounted for approximately 660,000 deaths in 2010, of which almost 86% were among children < 5 years of age.[1] Most malaria deaths (91%) and cases occur in Africa.[1] Significant improvements have been made over the past decade in reducing the incidence of malaria. Of the 99 countries with ongoing malaria transmission, 50 of these countries are on track to reduce the incidence of reported malaria cases by 75% by 2015.[2] Globally, over the past decade, malaria incidence has decreased by 17% and malaria-specific mortality rates have decreased by 26%.[2]

The principal malaria control interventions include vector control strategies, namely the distribution of long-lasting insecticide-treated nets and the application of indoor residual spraying (IRS), as well as increased use of rapid diagnostic tests (RDTs), first-line treatment of uncomplicated *Plasmodium falciparum* malaria with artemisinin-based combination therapy (ACT), and intermittent preventive treatment of malaria for pregnant women. Zambia, where this study was conducted, is a country in southern Africa with a high prevalence of malaria. Zambia was an early adopter of effective malaria control interventions, including ACTs as a first-line treatment, free RDTs, mass distribution of insecticide-treated nets (ITNs), and wide deployment of targeted IRS.[2,3]

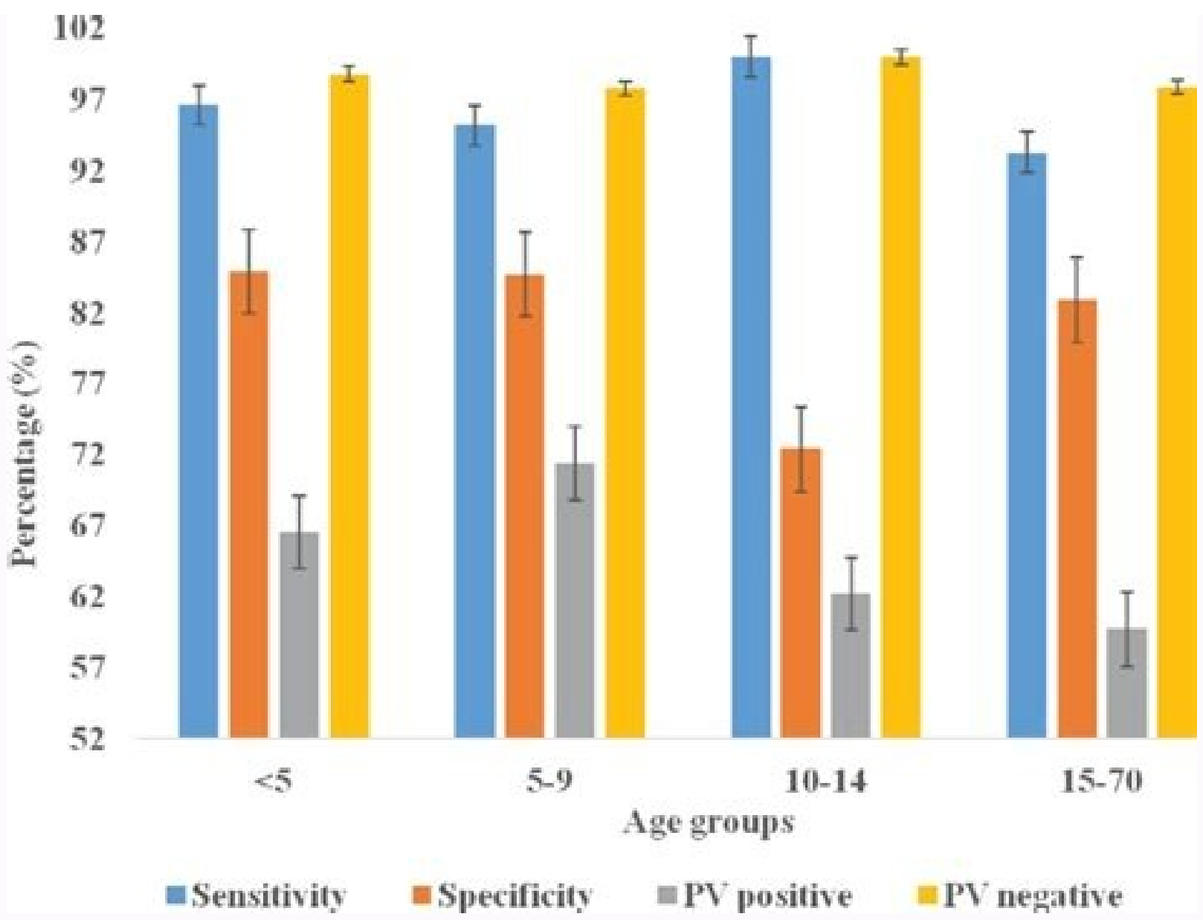
Compared with evidence on the effect of malaria control on mortality and morbidity outcomes, there is less evidence about the broader impact of malaria control on the health system, particularly at the service delivery level in terms of use of services and costs incurred. Various studies find that malaria inpatient admissions decrease with better malaria control strategies, but study results differ regarding the concurrent effect on admissions for other diseases.[4–7] Other studies have provided cost estimates for treating severe versus uncomplicated malaria cases, or assessed the cost effectiveness or cost savings at the health facility from a particular malaria control intervention.[8–11]

The purpose of this study was to assess how the implementation and scale-up of malaria control in the catchment area affects the health system by focusing specifically at the hospital level. We compare the number of inpatient admissions and outpatient visits for malaria during the pre-post period when malaria control interventions were scaled up in the relevant catchment areas. We also looked at how the proportion of inpatient admissions for malaria relative to admissions for other diseases changes over this period. Finally, we estimate the total yearly costs incurred at the facility level for treating malaria admissions during the pre-post period and assess how the proportion of costs for malaria admission relative to total hospital expenditures changes over time. Unlike other studies that have focused specifically on malaria control and its relationship with inpatient admissions, or its effect on the costs incurred at the facility, this study ties these different components together to provide a more comprehensive understanding of how malaria control affects the health facility in terms of admissions and costs.

BACKGROUND

Study areas and facility selection. Our study sites include two hospitals in the Southern Province of Zambia. These hospitals were selected because data were available during the period before significant scale-up of malaria control, thus enabling a pre-post comparison of malaria admissions and hospital costs.

*Address correspondence to Alison B. Comfort, Abt Associates, 55 Wheeler St., Cambridge, MA 02138. E-mail: alison_comfort@abtassoc.com



Rare but serious adverse drug reactions are therefore detected only in prospective phase IV post-marketing studies or population-based pharmacovigilance systems. When available, paediatric formulations and strengths are preferred, as they improve the effectiveness and accuracy of ACT dosing.Undesirable effects: There is some evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine may achieve lower plasma concentrations in infants than in older children and adults.Data available were not suitable for evaluation using the GRADE methodology.In most clinical studies, subgroups of infants and older children were not distinguished, and the evidence for young infants (< 5 kg) is insufficient for confidence in current treatment recommendations. The WHO Malaria RDT Product Testing programme provides comparative data on the performance of RDT products to guide procurement. knowlesi malariaResistance of P. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of P. Pending further information on excretion in breast milk, primaquine should not be used for nursing women, unless the breastfed infant has been checked for G6PD deficiency.Treat pregnant women with uncomplicated P. ovale [116] form hypnozoites, which are dormant parasite stages in the liver that cause relapse weeks to years after the primary infection. For example, in Thailand, despite low levels of malaria transmission, 8% of patients with acute vivax malaria also have P. SP, although considered safe, is not appropriate for use as an artesunate partner drug in many areas because of resistance to SP. Irrevalent in the Middle East, Asia, the Western Pacific and Central and South America. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.If the malaria species is not known with certainty, treat as for uncomplicated.Good practice statementIn areas with chloroquine-susceptible infections, treat adults and children with uncomplicated P. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.Desirable effects: There are no comparative trials of the efficacy or safety of primaquine in people with G6PD deficiency.Undesirable effects: Primaquine is known to cause haemolysis in people with G6PD deficiency.Of the 15 trials included in the systematic review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. In children with persistent fever despite parasite clearance, other possible causes of fever should be excluded, such as systemic Salmonella infections and urinary tract infections, especially in catheterized patients. With the exception of the Horn, it is rarer in Africa, where there is a high prevalence of the Duffy-negative phenotype, particularly in West Africa, although cases are reported in both Mauritania and Mali [114]. User- friendly packaging (e.g. blister packs) also encourages completion of a treatment course and correct dosing.The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.Good practice statementPharmacovigilance is the practice of monitoring the effects of medical drugs after they have been licensed for use, especially to identify and evaluate previously unreported adverse reactions. In comparison with no chemoprophylaxis: Chloroquine prophylaxis substantially reduced recurrent P. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 h). As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. Although many studies of the efficacy of antimalarial drugs have been conducted in populations and settings where malnutrition was prevalent, there are few studies of the disposition of the drugs specifically in malnourished individuals, and these seldom distinguished between acute and chronic malnutrition. falciparum malaria is endemic have progressively updated their treatment policy from use of monotherapy with drugs such as chloroquine, amodiaquine and sulfadoxine–pyrimethamine (SP) to the currently recommended artemisinin-based combination therapies (ACT). Microscopy technicians may also contribute to the diagnosis of non-malarial diseases.Although nucleic acid amplification-based tests are more sensitive, light microscopy is still considered the “field standard” against which the sensitivity and specificity of other methods must be assessed. The choice between RDTs and microscopy depends on local circumstances, including the skills available, the patient case-load, the epidemiology of malaria and use of microscopy for the diagnosis of other diseases. Mefloquine may cause adverse neuropsychiatric reactions and should not be prescribed for prophylaxis in patients with active or recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders. knowlesi may cause a fulminant disease similar to severe falciparum malaria (with the exception of coma, which does not occur) [123][124]. knowlesi, a simian parasite, causes occasional cases of malaria in or near forested areas of South-East Asia and the Indian subcontinent [115]. vivax (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT. Studies of the pharmacokinetics of SP used in IPTp in many sites show significantly decreased exposure to sulfadoxine, but the findings on exposure to pyrimethamine are inconsistent.Therefore, no dose modification is warranted at this time.Studies are available of the pharmacokinetics of artemether + lumefantrine, artesunate + mefloquine and dihydroartemisinin + piperaquine. Broad, inclusive stakeholder engagement in the design and implementation of national malaria control programmes will help to ensure they are feasible, appropriate, equitable and acceptable. A practical handbook on the pharmacovigilance of antimalarial medicines [145] provides a step-by-step approach for antimalarial pharmacovigilance. falciparum samples should be at least 75% at 200 parasites/μL.For detection of P. falciparum malaria, but the current evidence for young children is insufficient to be confident that the drug is as effective as currently recommended options. Options include increasing individual doses, changing the frequency or duration of dosing, or adding an additional antimalarial drug. Oral absorption of drugs may be reduced if there is diarrhoea or vomiting, or rapid gut transit or atrophy of the small bowel mucosa. Given intramuscularly, artemether may be absorbed more slowly and more erratically than water-soluble artesunate, which is absorbed rapidly and reliably after intramuscular injection. The exact duration of post-treatment follow-up is based on the elimination half- life of the partner drug in the ACT being evaluated. Light microscopy has other important advantages: low direct costs, if laboratory infrastructure to maintain the service is available;high sensitivity, if the performance of microscopy is high;differentiation of Plasmodia species;detection of gametocytaemia;allows monitoring of responses to therapy andcan be used to diagnose many other conditions.Good performance of microscopy can be difficult to maintain, because of the requirements for adequate training and supervision of laboratory staff to ensure competence in malaria diagnosis, electricity, good quality slides and stains, provision and maintenance of good microscopes and maintenance of quality assurance [85] and control of laboratory services.Numerous attempts have been made to improve malaria microscopy, but none has proven to be superior to the classical method of Giemsa staining and oil-immersion microscopy for performance in typical health care settings [86].Rapid diagnostic testsRapid diagnostic tests (RDTs) are immuno-chromatographic tests for detecting parasite-specific antigens in a finger-prick blood sample. The relationship between parasitaemia and risks depends on the epidemiological context: in higher-transmission settings, the risk of developing severe malaria in patients with high parasitaemia is lower, but “uncomplicated hyperparasitaemia” is still associated with a significantly higher rate of treatment failure.Patients with a parasitaemia of 4–10% and no signs of severity also require close monitoring, and, if feasible, admission to hospital. falciparum hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.Good practice statementIn falciparum malaria, the risk for progression to severe malaria with vital organ dysfunction increases at higher parasite densities. The ACTs are generally highly effective and well tolerated. Such recommendations are also designed to help the user to select and prioritize interventions from a range of potential alternatives. vivax malariaAlthough P. Antipyretics should be used if the core temperature is > 38.5 °C. In areas with pure P. Clear guidelines in the language understood by local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education and provision of information materials to shopkeepers and other dispensers can improve the understanding of malaria. Experimental studies on vivax malaria and the relapsing simian malaria P. falciparum malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.The WHO-approved first-line ACT options are: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.These options are recommended for adults and children, including infants, lactating women and pregnant women in their second and third trimester.In deciding which ACTs to adopt in national treatment policies, national policy- makers should take into account: the pattern of resistance to antimalarial drugs in the country, the relative efficacy and safety of the combinations, their cost, the availability of paediatric formulations and the availability of co-formulated products.Fixed-dose combinations are preferred to loose tablets or co-blistered products.The Guideline Development Group decided to recommend a “menu” of approved combinations from which countries can select first- and second- line therapies. falciparum in South-East Asia, which threatens these gains.Core principlesThe following core principles were used by the Guidelines Development Group that drew up the Guidelines for the Treatment of Malaria.1. Early diagnosis and prompt, effective treatment of malariaUncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment. Elsewhere, the dihydroartemisinin + piperaquine combination is highly effective.Resistance to SP limits its use in combination with artesunate to the few areas in which susceptibility is retained.Amodiaquine remains effective in combination with artesunate in parts of Africa and the Americas, although elsewhere resistance to this drug was prevalent before its introduction in an ACT.Considerations in use of artemisin-based combination therapyOral artemisinin and its derivatives (e.g. artesunate, artemether, dihydroartemisinin) should not be used alone. WHO’s position was published in the information note The use of artesunate-pyronaridine for the treatment of uncomplicated malaria [99] which clarifies that artesunate pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas.The pipeline for new antimalarial drugs is healthier than ever before, and several new compounds are in various stages of development. Mefloquine (5 mg/kg once a week) is recommended in areas where chloroquine resistance is common. When intramuscular injections can be given, the group recommends intramuscular artesunate in preference to rectal artesunate.This recommendation applies to all people with suspected severe malaria, including infants, lactating women and pregnant women in all trimesters.Where intramuscular artesunate is not available, use rectal artesunate (in children < 6 years), intramuscular artemether or intramuscular quinine.In the absence of direct comparative evaluations of parenteral antimalarial drugs for pre-referral treatment, the Guideline Development Group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for use in pre-referral situations. The lower efficacy may have been due to lower drug concentrations in pregnancy, as was also recently observed in a high-transmission area in Uganda and the United Republic of Tanzania. malariae.The blood stages of P. Studies to determine the best treatments for artemisinin-resistant malaria are needed urgently.It is strongly recommended that single-dose primaquine (as a gametocytocide) be added to all falciparum malaria treatment regimens as described in section 5.2.5. For the treatment of severe malaria in areas with established artemisinin resistance, it is recommended that parenteral artesunate and parenteral quinine be given together in full doses, as described in section 5.5.The two general classes of poor-quality medicines are those that are falsified (counterfeit), in which there is criminal intent to deceive and the drug contains little or no active ingredient (and often other potentially harmful substances), and those that are substandard, in which a legitimate producer has included incorrect amounts of active drug and/or excipients in the medicine, or the medicine has been stored incorrectly or for too long and has degraded. The problems of instability are accelerated under tropical conditions. falciparum, pan-specific or species-specific Plasmodium lactate dehydrogenase (pLDH) or pan-specific aldolase. In all such cases, empirical parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment.Treatment of severe malariaIt is essential that full doses of effective parenteral (or rectal) antimalarial treatment be given promptly in the initial treatment of severe malaria. Similarly, many pregnant women in Africa have been treated with amodiaquine alone or combined with SP or artesunate; however,amodiaquine use for the treatment of malaria in pregnancy has been formally documented in only > 1300 pregnancies. If both the slide examination and the RDT results are negative, malaria is extremely unlikely, and other causes of the illness should be sought and treated.This document does not include recommendations for use of specific RDTs or for interpreting test results. GMP will revise the Guidelines based on new information available in 2021.Arterolane + piperaquine is a combination of a synthetic ozonide and piperaquine phosphate that is registered in India. knowlesi should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.Mixed malaria infectionsMixed malaria infections are common in endemic areas. The practical consequence is that two packs of an antimalarial drug might have to be opened to ensure adequate treatment. If the suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and the buttocks held together for 10 min to ensure retention of the dose.Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where possible, however, blood smears should be examined by microscopy, with frequent monitoring of parasitaemia (e.g. every 12 h) during the first 2–3 days of treatment in order to monitor the response.Choosing ACTIn the absence of resistance, all the recommended ACTs have been shown to result in parasitological cure rates of > 95%. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.--Current methods do not distinguish recrudescence from relapse or relapse from newly acquired infection, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin is < 10% within 28 days.When primaquine is not given for radical cure, slowly eliminated ACT that prevents recurrent parasitemia before day 28 should be used (dihydroartemisinin + piperaquine or artesunate + mefloquine).Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. Recurrent vivax malaria is an important impediment to human and economic development in affected populations. Modelling studies suggest that having multiple first-line ACTs available for use may help to prevent or delay the development of resistance.Recommendation: Dihydroartemisinin + piperaquine is recommended for general use.A systematic review showed that the dosing regimen of dihydroartemisinin + piperaquine currently recommended by the manufacturers leads to suboptimal dosing in young children. vivax epidemics, ACTs or chloroquine (if prevalent strains are sensitive)

should be used.Anti-relapse therapy for P. In principle, dosing of large adults should be based on achieving the target mg/kg bw dose for each antimalarial regimen. In particular, more data are urgently needed on the safety of ACTs during the first trimester of pregnancy and on potential interactions between antimalarial and other commonly used medicines.These guidelines provide a generic framework for malaria diagnosis and treatment policies worldwide; however, national policy-makers will be required to adapt these recommendations on the basis of local priorities, malaria epidemiology, parasite resistance and national resources.National decision-makingNational decision-makers are encouraged to adopt inclusive, transparent, rigorous approaches. In the absence of further information, prophylactic anticonvulsants are not recommended.Treatments that are not recommendedIn an attempt to reduce the high mortality from severe malaria, various adjunctive treatments have been evaluated, but none has proved effective and many have been shown to be harmful. Patients or caregivers should be informed that this ACT should be taken immediately after food or a fat containing drink (e.g. milk), particularly on the second and third days of treatment.Artesunate + amodiaquineFormulations currently available: A fixed-dose combination in tablets containing 25 + 67.5 mg, 50 + 135 mg or 100 + 270 mg of artesunate and amodiaquine, respectivelyTarget dose and range: The target dose (and range) are 4 (2–10) mg/kg bw per day artesunate and 10 (7.5–15) mg/kg bw per day amodiaquine once a day for 3 days. Heparin, prostacyclin, desferroxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin anti-TNF antibody, cyclosporine A,dichloroacetate, adrenaline, hyperimmune serum,N-acetylcysteine and bolus administration of albumin are not recommended.In addition,use of corticosteroids increases the risk for gastrointestinal bleeding and seizures and has been associated with prolonged coma resolution times when compared with placebo.Treatment of severe malaria during pregnancyWomen in the second and third trimesters of pregnancy are more likely to have severe malaria than other adults, and, in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. RDTs are relatively simple to perform and to interpret, and they do not require electricity or special equipment [90].Since 2012, WHO has recommended that RDTs should be selected in accordance with the following criteria, based on the results of the assessments of the WHO Malaria RDT Product Testing programme [91]: For detection of P. Fixed-dose combinations encourage adherence and are preferred to loose (individual) tablets. In some countries, the group adapting the guidelines for national use might have to re-evaluate the global evidence base with respect to their own context. Where both P. falciparum malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.Good practice statementMore data are available on use of artemether + lumefantrine with antiretroviral treatment. falciparum. vivax and the two species of P. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.Management of complicationsSevere malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown below.Immediate clinical management of severe manifestations and complications of P. falciparum malaria [120][121]. Fetal death and premature labour are common.Parenteral antimalarial drugs should be given to pregnant women with severe malaria in full doses without delay. Bedrooms should be sprayed with an aerosol insecticide at dusk. ovale, P. falciparum malaria in infants and young children can have fatal consequences, particularly for more severe infections. The current assessment of risk–benefit suggests that ACTs should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy.The current standard six-dose artemether + lumefantrine regimen for the treatment of uncomplicated falciparum malaria has been evaluated in > 1000 women in the second and third trimesters in controlled trials and has been found to be well tolerated and safe. Although providers of care may be willing to perform diagnostic tests, they do not, however, always respond appropriately to the results. The revised parenteral dose regimens are predicted to provide equivalent artesunate and dihydroartemisinin exposures across all age groups.Individual parenteral artesunate doses between 1.75 and 4 mg/kg have been studied and no toxicity has been observed. It has a daily asexual cycle, resulting in a rapid replication rate and high parasitaemia. The trials were conducted in various African and Asian countries between 1989 and 2010.In comparison with quinine, parenteral artesunate: reduced mortality from severe malaria by about 40% in adults (RR, 0.61; 95% CI, 0.50–0.75, five trials, 1664 participants, high-quality evidence);reduced mortality from severe malaria by about 25% in children (RR, 0.76; 95% CI, 0.65–0.90, four trials, 5765 participants, high-quality evidence); andwas associated with a small increase in neurological sequelae in children at the time of hospital discharge (RR, 1.36; 95% CI, 1.01–1.83, three trials, 5163 participants, moderate-quality evidence), most of which, however, slowly resolved, with little or no difference between artesunate and quinine 28 days later (moderate-quality evidence).The guideline development group considered that the small increase in neurological sequelae at discharge after treatment with artesunate was due to the delayed recovery of the severely ill patients, who would have died had they received quinine. The two methods used routinely for parasitological diagnosis of malaria are light microscopy and immunochromatographic RDTs. The latter detect parasite-specific antigens or enzymes that are either genus or species specific.Both microscopy and RDTs must be supported by a quality assurance programme. Co-infection with other species is common.DiagnosisDiagnosis of P. Artemether can be given as an oil-based intramuscular injection or orally. falciparum transmissibility.The population benefits of reducing malaria transmission with gametocytocidal drugs such as primaquine require that a very high proportion of treated patients receive these medicines and that there is no large transmission reservoir of asymptomatic parasite carriers. In the majority of cases of persistent fever, however, no other pathogen is identified after parasite clearance. vivax malaria (RR, 0.02; 95% CI, 0.00–0.26, one trial, 951 participants, moderate- quality evidence).Primaquine is contraindicated in pregnant or breastfeeding women with P. None of the trials reported serious or treatment-limiting adverse events.Overall certainty of evidence for all critical outcomes: very low.In a systematic review of primaquine for radical cure of P. Simulations of artesunate and dihydroartemisinin exposures were conducted for each age group. Primaquine should be avoided in the first 6 months of life (although there are no data on its toxicity in infants), and tetracyclines should be avoided throughout infancy. Sleeping under insecticide-treated (permethrin 0.2 g/m2 of material every 6 mo) mosquito nets is perhaps the most beneficial antimalarial measure available. P. The WHO Guidelines for the treatment of malaria were first developed in 2006 and have been revised periodically, with the most recent edition published in 2015. If the seizures continue, the airways should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). vivax in all transmission settings the panel detection score against P. This has contributed substantially to reductions in global morbidity and mortality from malaria. Prescribers should take the time necessary to explain to patients why they should complete antimalarial course.Artemether + lumefantrineFormulations currently available: Dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine, and standard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. It is not necessary to perform an electrocardiogram before prescribing dihydroartemisinin + piperaquine, but this ACT should not be used in patients with congenital QT prolongation or who have a clinical condition or are on medications that prolong the QT interval. Referral may be necessary anyway to obtain second-line treatment. The patient should be weighed or body weight estimated, so that medicines, including antimalarial drugs and fluids, can be given appropriately. Initial rectal or parenteral treatment must always be followed by a full 3-day course of ACT.Use of antipyreticsIn young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. malariae and P.ovale; andthe heterogeneous quality of commercially available products and the existence of lot-to-lot variation.In a systematic review [93], the sensitivity and specificity of RDTs in detecting P. Severe malaria may also present immediately after delivery. The available data are sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception). falciparum malaria can result from re-infection or recrudescence (treatment failure). Since 2008, 210 products have been evaluated in five rounds of product testing [91][94].For the diagnosis of severe malaria, microscopy is preferred, as it provides a diagnosis of malaria and assessment of other important parameters of prognostic relevance in severely ill patients (such as parasite count and stage of parasite development and intra-leukocyte pigment). Outside South-East Asia, there is no convincing evidence yet for reduced susceptibility to the artemisinins; therefore, the performance of the partner drug is the main determinant in the choice of ACT, according to the following principles: Drugs used in IPTp, SMC or chemoprophylaxis should not be used as first-line treatment in the same country or region.Resistance to SP limits use of artesunate + SP to areas in which susceptibility is retained.Thus, in the majority of malaria-endemic countries, first-line ACTs remain highly effective, although resistance patterns change over time and should be closely monitored.Choosing among formulationsUse of fixed-dose combination formulations will ensure strict adherence to the central principle of combination therapy. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Nevertheless despites these uncertainties, infants need prompt, effective treatment of malaria. This should not be interpreted as a sign of neurotoxicity. In one large series, this effect increased with successive pregnancies [122].P. In Papua province, Indonesia [118], and in Papua New Guinea [119], where malaria transmission is intense, P. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. vivax mono-infections has not been compared directly in trials with use of artesunate + mefloquine.Resistance of P. Single-dose atovaquone–proguanil with efavirenz, lopinavir–ritonavir or atazanavir–ritonavir were all associated with a significantly decreased area under the concentration–time curve for atovaquone (two- to fourfold) and proguanil (twofold), which could well compromise treatment or prophylactic efficacy. Blood should be taken for cross-matching, a full blood count, a platelet count, clotting studies, blood culture and full biochemistry (if possible). ovale and P. In addition, there are several new generic formulations of existing drugs. Recent evidence suggests that, in endemic areas where people are inoculated frequently with P. Close monitoring is required. In areas of stable endemic malaria, HIV-infected patients who are partially immune to malaria may have more frequent, higher-density infections, while in areas of unstable transmission, HIV infection is associated with increased risks for severe malaria and malaria-related deaths. The antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil.The safest treatment regimen for pregnant women in the first trimester with uncomplicated falciparum malaria is therefore quinine + clindamycin (10mg/kg bw twice a day) for 7 days (or quinine monotherapy if clindamycin is not available). Clothes can also be treated with an insecticide, such as permethrin, which is safe for this purpose. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. All patients with suspected malaria should be treated on the basis of a confirmed diagnosis by microscopy examination or RDT testing of a blood sample. None of these yet has a sufficient evidence base for general recommendation (i.e. unrestricted use).A systematic review of artesunate + pyronaridine included six trials with a total of 3718 patients. They judged the accumulated indirect evidence to be sufficient to recommend parenteral artesunate rather than intramuscular artemether for use in all age groups.--Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?Intramuscular artemether should be considered only when parenteral artesunate is not available.Treat children and adults with severe malaria with parenteral artesunate for at least 24 h.Strength of recommendation: Strong for.Indirect comparisons of artesunate and quinine and of artemether and quinine were considered by the Guideline Development Group, with what is known about the pharmacokinetics of the two drugs. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or is associated with only mild, non-specific symptoms. falciparum malaria. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. Rapid bolus infusion of colloid or crystalloids is contraindicated. There is no consensus on the indications, benefits and dangers involved or on practical details such as the volume of blood that should be exchanged. malariae and P. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.Duration of ACT treatment: ACT regimens should provide 3 days' treatment with an artemisinin derivative.Strong recommendation, high-certainty evidenceDesirable effectsFewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the first 28 days (high-quality evidence).Fewer participants taking ACTs containing 3 days of an artemisinin derivative have gametocytaemia at day 7 (high-quality evidence).For all critical outcomes: High.In four randomized controlled trials in which the addition of 3 days of artesunate to SP was compared directly with 1 day of artesunate with SP: Three days of artesunate reduced the PCR-adjusted treatment failure rate within the first 28 days from that with 1 day of artesunate (RR, 0.45; 95% CI, 0.36–0.55, four trials, 1202 participants, high-quality evidence).Three days of artesunate reduced the number of participants who had gametocytaemia at day 7 from that with 1 day of artesunate (RR, 0.74; 95% CI, 0.58–0.93, four trials, 1260 participants, high-quality evidence).The guideline development group considered that 3 days of artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk of drug resistance resulting from incomplete treatment.Longer ACT treatment may be required to achieve > 90% cure rate in areas with artemisinin-resistant P. Therefore, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then treat with 14 days of primaquine to prevent future relapse.Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. Furthermore, artesunate is simpler and safer to use.Pre-referral treatment optionsSee recommendation.Adjustment of parenteral dosing in renal failure or hepatic dysfunctionThe dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. G6PD deficiency is an inherited sex-linked genetic disorder, which is associated with some protection against P. Treatment of P. It is therefore recommended that patients, particularly young children, be treated with a first dose of one of the recommended treatments before referral (unless the referral time is 10% on day 28.Treat pregnant women in their first trimester who have chloroquine-resistant P. falciparum parasites, making HRP2-based tests not suitable in this region [92];poor sensitivity for detecting P. A skilled microscopist can detect asexual parasites at a density of < 10 per µL of blood, but under typical field conditions, the limit of sensitivity is approximately 100 parasites per µL [84]. vivax hypnozoites, which explains why P. The available evidence for artemether + lumefantrine, SP and chloroquine does not indicate dose modification at this time, but young children should be closely monitored, as reduced drug exposure may increase the risk for treatment failure. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.DefinitionsSevere falciparum malaria: For epidemiological purposes, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of P. There is no need for them to have their pregnancy interrupted because of this exposure.In the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.Previous data indicated that the antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil. The flavoured dispersible tablet paediatric formulation facilitates use in young children.Target dose range: A total dose of 5–24 mg/kg bw of artemether and 29–144 mg/ kg bw of lumefantrineRecommended dosage regimen: Artemether + lumefantrine is given twice a day for 3 days (total, six doses). Resistance to both components has compromised the efficacy of artesunate + mefloquine in western Cambodia, eastern Myanmar and eastern Thailand.Lumefantrine shares some cross-resistance with mefloquine, but this has not compromised its efficacy in any of the areas in which artemether + lumefantrine has been used outside South-East Asia.Until recently, there was no evidence of resistance to piperaquine anywhere, but there is now reduced susceptibility in western Cambodia. The requirement for stringent quality standards is particularly important for this class of compounds. There is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial agents in pregnancy, particularly during the first trimester.First trimester of pregnancySee Justification under recommendation.Second and third trimestersExperience with artemisinin derivatives in the second and third trimesters (over 4000 documented pregnancies) is increasingly reassuring: no adverse effects on the mother or fetus have been reported. The guideline development group therefore recommended lowering the age restriction to 6 months.Desirable effects: Chloroquine prophylaxis reduced recurrent P. Primaquine generates reactive intermediate metabolites that are oxidant and cause variable haemolysis in G6PD-deficient individuals. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. malariae malaria is based on microscopy. Arterolane + piperaquine, artemisinin + piperaquine base and artemisinin + napththoquine are new ACTs, which are registered and used in some countries. The revised dose regimens are predicted to provide equivalent piperaquine exposures across all age groups.This dose adjustment is not predicted to result in higher peak piperaquine concentrations than in older children and adults, and as there is no evidence of increased toxicity in young children, the GRC concluded that the predicted benefits of improved antimalarial exposure are not at the expense of increased risk.Recurrence of P. High-quality light microscopy requires well-trained, skilled staff, good staining reagents, clean slides and, often, electricity to power the microscope. vivax relapses at 3-week intervals and is more resistant to primaquine. To optimize the benefits of effective treatment, wide dissemination of national treatment guidelines, clear recommendations, appropriate information, education and communication materials, monitoring of the deployment process, access and coverage, and provision of adequately packaged antimalarial drugs are needed.Community case management of malariaCommunity case management is recommended by WHO to improve access to prompt, effective treatment of malaria episodes by trained community members living as close as possible to the patients. At the current levels of resistance, the artemisinin derivatives still provide significant antimalarial activity; therefore, longer courses of treatment with existing or new augmented combinations or treatment with new partner medicines (e.g. artesunate + pyronaridine) may be effective. Paediatric formulations are currently available for artemether + lumefantrine, dihydroartemisinin + piperaquine and artesunate + mefloquine.Other operational issues in managing effective treatmentIndividual patients derive the maximum benefit from an ACT if they can access it within 24–48 h of the onset of malaria symptoms. Following parenteral artesunate, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). They may be impossible to distinguish at points of care from the genuine product and may lead to under-dosage and high levels of treatment failure, giving a mistaken impression of resistance, or encourage the development of resistance by providing sub-therapeutic blood levels. Both are at higher risk for severe malaria. Rectal administration of a single dose of artesunate as pre-referral treatment reduces the risks for death and neurological disability, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in hospital. Postpartum bacterial infection is a common complication and should be managed appropriately.Treatment of severe P. If this approach is used, it is imperative to monitor intermittently the prevalence of malaria as a true cause of fever and revise the policy appropriately. Thus, to optimize the benefits of deploying ACTs, they should be available in the public health delivery system, the private sector and the community, with no financial or physical barrier to access. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Prescribers, shopkeepers and vendors should therefore give clear, comprehensible explanations of how to use the medicines. Nevertheless, women in early pregnancy will often be exposed inadvertently to the available first-line treatment, mostly ACT. Some novel antimalarial agents are already registered in some countries. vivax, P. The distribution and use of oral artesunate monotherapy outside special centres is strongly discouraged, and quinine-containing regimens are not well tolerated.Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. Relapse-free efficacy at 6 months was 89.2% with tafenoquine 300 mg and 91.9% with tafenoquine 600 mg compared with chloroquine alone (37.5%). Heterozygote females with higher mean red cell activities may still show substantial haemolysis. Fixed-dose artesunate + amodiaquine performs better than loose tablets, presumably by ensuring adequate dosing. falciparum asexual parasitaemia.Impaired consciousness: A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in childrenProstration: Generalized weakness so that the person is unable to sit, stand or walk without assistanceMultiple convulsions: More than two episodes within 24 hAcidosis: A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anaemia) and others with higher mortality rates (e.g. acidosis). Malaria RDTs should be used if quality-assured malaria microscopy is not readily available. vivax tend to peak at a younger age than for P. Patients who present with malaria should be asked this question routinely.The recommended second-line treatment is an alternative ACT known to be effective in the region. The displacement of large numbers of people with little or no immunity within malaria-endemic areas increases the risk for malaria epidemics among the displaced population, while displacement of people from an endemic area to an area where malaria has been eliminated can result in re-introduction of transmission and a risk for epidemics in the resident population.Climate change may also alter transmission patterns and the malaria burden globally by producing conditions that favour vector breeding and there by increasing the risks for malaria transmission and epidemics.Parasitological diagnosis during epidemicsIn the acute phase of epidemics and complex emergency situations, facilities for laboratory diagnosis with good-quality equipment and reagents and skilled technicians are often not available or are overwhelmed. In Cambodia, where artemisinin resistance is worst, none of the currently recommended treatment regimens provides acceptable cure rates (> 90%), and continued use of ineffective drug regimens fuels the spread of resistance. In addition, it granted a positive scientific opinion for artesunate-pyronaridine granules for the treatment of children with a body weight of 5–20 kg. falciparum, but the latter are slightly more specific because the HRP2 antigen may persist in blood for days or weeks after effective treatment. Elsewhere, there is no convincing evidence for reduced susceptibility to the artemisinins; therefore, the performance of the partner drugs is the determining factor in the choice of ACT, and the following principles apply: Resistance to mefloquine has been found in parts of mainland South-East Asia where this drug has been used intensively. In the past chloroquine resistant parasites emerged near the Cambodia–Thailand border and then spread throughout Asia and Africa at a cost of millions of lives. Further trials would provide clarification but are unlikely to be done. Although there are minor differences in the oral absorption, bioavailability and tolerability of the different artemisinin derivatives, there is no evidence that these differences are clinically significant in currently available formulations. vivax prevalent in East Asia and Oceania. The criteria for selecting RDTs or microscopy can be found in the WHO Recommended selection criteria for the procurement of malaria rapid diagnostic tests [94].Diagnosis with either microscopy or RDTs is expected to reduce overuse of antimalarial medicines by ensuring that treatment is given only to patients with confirmed malaria infection, as opposed to treating all patients with fever [95]. If adequate records are kept, therapy can be given in the post-epidemic period to patients who have been treated with blood schizontocides.Malaria elimination settingsUse of gametocytocidal drugs to reduce transmissionACT reduces P. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT.Strong recommendation, high-certainty evidenceArtesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. If available, haemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. falciparum malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.*unGRADEd recommendation, anticipated to be updated in 2021The pharmacokinetics properties of many medicines in infants differ markedly from those in adults because of the physiological changes that occur in the first year of life. Antimalarial treatment should be limited to cases with positive tests, and patients with negative results should be reassessed for other common causes of fever and treated appropriately.In nearly all cases of symptomatic malaria, examination of thick and thin blood films by a competent microscopist will reveal malaria parasites. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.Clinical assessmentSevere malaria is a medical emergency. Some tests allow detection of only one species (P. vivax malaria, dihydroartemisinin + piperaquine provided a longer prophylactic effect than ACTs with shorter half-lives (artemether + lumefantrine, artesunate + amodiaquine), with significantly fewer recurrent parasitaemias during 9 weeks of follow-up (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants). Studies on adherence suggest that 3-day regimens of medicines such as ACTs are completed reasonably well, provided that patients or caregivers are given an adequate explanation at the time of prescribing or dispensing. This is because each P. falciparum infections, and one third of acute P. If there is no improvement in the patient's condition within 48 h, the dose should be reduced by one third, i.e. to 10 mg salt/kg bw every 12 h.Rapid intravenous administration of quinine is dangerous. vivax coexist, intensive malaria control often has a greater effect on P. Cryptic P. When scored tablets are not available, 5 mg tablets can be used.Therapeutic dose: 0.25–0.5 mg/kg bw per day primaquine once a day for 14 days.Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. It requires a quality assurance system, which is often not well implemented in malaria-endemic countries.In many areas, malaria patients are treated outside the formal health services, e.g. in the community, at home or by private providers. For older children and adults, the recommended pre-referral treatment options, in descending order of preference, are intramuscular injections of artesunate; artemether; and quinine.Administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable even at community level. RDTs for detecting PfHRP2 can be useful for patients who have received incomplete antimalarial treatment, in whom blood films can be negative. In a low-transmission setting on the Myanmar–Thailand border,however,the efficacy of the standard six-dose artemether + lumefantrine regimen was inferior to 7 days of artesunate monotherapy. falciparum transmission has been widely used in low transmission settings.Use of primaquine as a P.falciparum gametocytocide has a particular role in programmes to eliminate P.falciparum malaria.The population benefits of reducing malaria transmission by gametocytocidal drugs require that a high proportion of patients receive these medicines. Unfortunately, resistance to artemisinins has arisen recently in P. The artemisinin component rapidly clears parasites from the blood (reducing parasite numbers by a factor of approximately 10 000 in each 48 h asexual cycle) and is also active against the sexual stages of the gametocytes that mediate onward transmission to mosquitos. The difference is no longer evident on day 28 after discharge (moderate-quality evidence).Overall certainty of evidence for all critical outcomes: high.In a systematic review of artesunate for severe malaria [132], eight randomized controlled trials with a total of 1664 adults and 5765 children, directly compared parenteral artesunate with parenteral quinine. When the seizure has stopped, the child should be treated as indicated in section 7.10.5, if his or her core temperature is > 38.5 °C. Therapy should be started a week before entering a malarious area and continued for 4 weeks after leaving it. In the absence of data, treatment providers should attempt to follow up the treatment outcomes of large adults whenever possible.Malaria in pregnancy is associated with low-birth-weight infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. The group noted the small absolute prolongation of the QT interval with dihydroartemisinin + piperaquine but was satisfied that the increase was of comparable magnitude to that observed with chloroquine and was not important clinically.A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Vaccines against various malarial antigens have been tried for many years, all around the world. Anti-emetics are potentially sedative and may have neuropsychiatric adverse effects, which could mask or confound the diagnosis of severe malaria. They are at increased risk for severe malaria and for treatment failure and are considered an important source of antimalarial drug resistance.People with P. Consequently, higher doses of primaquine have been used (0.375–0.5 mg base/kg bw per day), but there are few data from comparative trials.Primaquine is contraindicated in pregnancy and lactation < 6 months post partum, unless the infant has been tested for G6PD deficiency. ovale, and P. The target doses and ranges for children weighing < 25 kg are 4 (2.5–10) mg/kg bw per day dihydroartemisinin and 24 (20–32) mg/kg bw per day piperaquine once a day for 3 days.Recommended dosage regimen: The dose regimen currently recommended by the manufacturer provides adequate exposure to piperaquine and excellent cure rates (> 95%), except in children < 5 years, who have a threefold increased risk for treatment failure. The impact in reducing transmission at a population level depends on high coverage rates and the transmission intensity. falciparum infections in endemic areas where both parasites are prevalent. Ibuprofen (5 mg/kg bw) has been used successfully as an alternative in the treatment of malaria and other childhood fevers, but, like aspirin and other non-steroidal anti-inflammatory drugs, it is no longer recommended because of the risks of gastrointestinal bleeding, renal impairment and Reye's syndrome.Use of anti-emeticsVomiting is common in acute malaria and may be severe. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.Desirable effects: ACTs clear parasites more quickly than chloroquine (high-quality evidence).ACTs with long half-lives provide a longer period of suppressive post-treatment prophylaxis against relapses and new infections (high-quality evidence).Simplified national protocols for all forms of uncomplicated malaria.Adequate treatment of undiagnosed P. There are many (> 180) different G6PD deficiency genetic variants; nearly all of which make the red cells susceptible to oxidant haemolysis, but the severity of haemolysis may vary. Recommendations for the doses of this and other antimalarial agents should state clearly whether the salt or the base is being referred to; doses with different salts must have the same base equivalents. Unconscious patients should undergo a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate concentration should be measured, if possible. In the absence of exposure to primaquine or another oxidant agent, G6PD deficiency rarely causes clinical manifestationsso, many patients are unaware of their G6PD status. The particular advantage of artemisinins over other antimalarial drugs is that they kill circulating ring-stage parasites and thus accelerate therapeutic responses.This is lost in resistance to artemisinin.As a consequence, parasite clearance is slowed, and ACT failure rates and gametocytaemia both increase.The reduced efficacy of artemisinin places greater selective pressure on the partner drugs,to which resistance is also increasing.This situation poses a grave threat. falciparum in blood samples from patients in endemic areas attending ambulatory health facilities with symptoms suggestive of malaria were compared with the sensitivity and specificity of microscopy or polymerase chain reaction. vivax has become resistant to SP more rapidly than P. Patients who are heavy but not obese require the same mg/kg bw doses as lighter patients.In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. This is particularly likely if the patient received a recent dose of an artemisinin derivative. Co-formulation probably contributes importantly to adherence. Thus, where indicated a single dose of 0.25mg/kg bw of primaquine base should be given on the first day of treatment, in addition to an ACT, to all patients with parasitologically confirmed P.falciparum malaria except for pregnant women, infants < 6 months of age and women breastfeeding infants < 6 months of age, because there are insufficient data on the safety of its use in these groups.Dosing table based on the most widely currently available tablet strength (7.5mg base)View in own windowaDosing of young children weighing < 10 kg is limited by the tablet sizes currently available.Please refer to the Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria [110].Desirable effectsSingle doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds (moderate-quality evidence).There are too few trials of doses < 0.4 mg/kg bw to quantify the effect on gametocyte carriage (low-quality evidence).Analysis of observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.Undesirable effectsPeople with severe G6PD deficiency are at risk for haemolysis. knowlesi should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.Mixed malaria infections are common in endemic areas. The only antimalarial agent that is currently contraindicated for infants (80% of normal) can be differentiated only with a quantitative test. Falsified antimalarial tablets and ampoules containing little or no active pharmaceutical ingredients are a major problem in some areas. In a large, double-blind, placebo-controlled evaluation of a single prophylactic intramuscular injection of 20 mg/kg bw of phenobarbital to children with cerebral malaria, the frequency of seizures was reduced but the mortality rate was increased significantly. Adjustments to previous dosing regimens for dihydroartemisinin + piperaquine in uncomplicated malaria and for artesunate in severe malaria are now recommended to improve the drug exposure in this vulnerable population. The only trial of rectal artesunate as pre-referral treatment showed the expected reduction in mortality of young children but unexpectedly found increased mortality in older children and adults. Infants younger than 6 weeks should not be administered chemoprophylaxis. Chemoprophylaxis is undermined by poor adherence and parasite resistance to almost all drugs, and is not fully dependable on its own. In only one study, conducted in Indonesia, was resistance to chloroquine reported in P. For obese patients, less drug is often distributed to fat than to other tissues; therefore, they should be dosed on the basis of an estimate of lean body weight, ideal body weight. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. The rates of treatment failure are substantially higher in hyperparasitaemic patients and patients in areas with artemisinin-resistant falciparum malaria, and these groups require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations) than is achieved with current ACT dosage recommendations. However quinine accumulates in severe vital organ dysfunction. A similar temporal pattern of recurrence with each of the drugs is seen in the P. The combined data are insufficient to justify dose adjustment. Therefore, their response to artesunate + amodiaquine treatment should be closely monitored.Artesunate + amodiaquine is associated with severe neutropenia, particularly in patients co-infected with HIV and especially in those on zidovudine and/or cotrimoxazole. vivax malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in P. Exposure to lumefantrine and other non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment, namely nevirapine and etravirine, did not show consistent changes that would require dose adjustment.Studies of administration of quinine with lopinavir–ritonavir or ritonavir alone in healthy volunteers gave conflicting results. Approval was based on an international programme of over 4000 participants. falciparum and P. An additional advantage of lengthening the duration of treatment (by giving a 5-day regimen) is that it provides additional exposure of the asexual cycle to the artemisinin component as well as augmenting exposure to the partner drug. If this is not possible, it should be given by intramuscular injection to the anterior thigh; quinine should not be injected into the buttock in order to avoid sciatic nerve injury. Lower total doses are not recommended, as these encourage the emergence of resistance. It also causes methemoglobinaemia. This resulted from respiratory arrest and was associated with additional use of benzodiazepine.A 20 mg/kg bw dose of phenobarbital should not be given without respiratory support. At this dose, however, the risk is thought to be small; there are insufficient data to quantify this risk.Overall certainty of evidence for all critical outcomes: low.In an analysis of observational studies of single-dose primaquine, data from mosquito feeding studies on 180 people suggest that adding 0.25 mg/kg primaquine to treatment with an ACT can rapidly reduce the infectivity of gametocytes to mosquitoes.In a systematic review of eight randomized controlled trials of the efficacy of adding single-dose primaquine to ACTs for reducing the transmission of malaria, in comparison with ACTs alone [107]: single doses of > 0.4 mg/kg bw primaquine reduced gametocyte carriage at day 8 by about two thirds (RR, 0.34; 95% CI, 0.19–0.59, two trials, 269 participants, high-certainty evidence); andsingle doses of primaquine > 0.6 mg/kg bw reduced gametocyte carriage at day 8 by about two thirds (RR, 0.29; 95% CI, 0.22–0.37, seven trials, 1380 participants, high-certainty evidence).There have been no randomized controlled trials of the effects on the incidence of malaria or on transmission to mosquitos.The guideline development group considered that the evidence of a dose– response relation from observational studies of mosquito feeding was sufficient to conclude the primaquine dose of 0.25mg/kg bw significantly reduced P. It differs from previous treatments in that the piperaquine is in the base form, the artemisinin dose is relatively low, and the current recommendation is for only a 2-day regimen. Although several RDTs allow diagnosis of both P. WHO guidelines contain recommendations on clinical practice or public health policy intended to guide end-users as to the individual or collective actions that can or should be taken in specific situations to achieve the best possible health outcomes. vivax malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.Prompt effective treatment and case management should be the same as for severe P. falciparum to distinguish between recrudescence (true treatment failure) and new infections.An antimalarial medicine that is recommended in the national malaria treatment policy should be changed if the total treatment failure proportion is ≥ 10%, as assessed in vivo by monitoring therapeutic efficacy. Countries where chloroquine is used for treatment of vivax malaria should monitor for chloroquine resistance and change to ACT when the treatment failure rate is > 10% at day 28.Current methods cannot distinguish recrudescence from relapse or relapse from newly acquired infections, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin are < 10%.Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. They will increase the likelihood of better prescribing and adherence, appropriate referral and unnecessary use of antimalarial medicines.Adherence to treatmentPatient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision. While age-based dosing may be more practical in children, the relation between age and weight differs in different populations. A lower dose of folate (0.4–0.5 mg bw/day) or a treatment other than artesunate + SP should be used.Mefloquine is considered safe for the treatment of malaria during the second and third trimesters; however,it should be given only in combination with an artemisinin derivative.Quinine is associated with an increased risk for hypoglycaemia in late pregnancy,and it should be used (with clindamycin) only if effective alternatives are not available.Primaquine and tetracyclines should not be used in pregnancy.Dosing in pregnancyData on the pharmacokinetics of antimalarial agents used during pregnancy are limited. Resistance to antimalarial drugs arises because of selection of parasites with genetic changes (mutations or gene amplifications) that confer reduced susceptibility. Although many women in the second and third trimesters of pregnancy in Africa have been exposed to artemether + lumefantrine, further studies are under way to evaluate its efficacy, pharmacokinetics and safety in pregnant women. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. The frequency and pattern of relapses varies geographically, with relapse rates generally ranging from 8% to 80%. A full course of radical treatment with primaquine should be given after recovery.Please refer to Management of severe malaria - A practical handbook, 3rd edition [131].Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. A further meeting in December 2017 resulted in the need for GMP to request, in 2018, the support of the WHO Advisory Committee on Saftey of Medicinal Products to conduct an independent expert review of all available data and information. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Interim phase 3 trial results have been reported for the malaria vaccine RTS,S/AS01. Med Trop (Mars). HRP2-detecting RDTs are not suitable for detecting treatment failure. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.Please refer to Rectal artesunate for pre-referral treatment of severe malaria [138].Desirable effects: No studies of direct comparison of rectal artesunate with parenteral antimalarial drugs for pre-referral treatment.In hospital care, parenteral artesunate reduces the number of deaths to a greater extent than parenteral quinine (high-quality evidence) and probably reduces the number of deaths from that with intramuscular artemether (moderate-quality evidence).Overall certainty of evidence for all critical outcomes: moderate.In a systematic review of pre-referral treatment for suspected severe malaria, in a single large randomized controlled trial of 17 826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, pre-referral rectal artesunate was compared with placebo [137].In comparison with placebo: Rectal artesunate reduced mortality by about 25% in children < 6 years (RR, 0.74; 95% CI, 0.59–0.93; one trial, 8050 participants, moderate- quality evidence).Rectal artesunate was associated with more deaths in older children and adults (RR, 2.21; 95% CI, 1.18–4.15; one trial 4018 participants, low- quality evidence).The guideline development group could find no plausible explanation for the finding of increased mortality among older children and adults in Asia who received rectal artesunate, which may be due to chance. vivax) or pan-malarial antigens (Pan-pLDH or aldolase).Light microscopyMicroscopy not only provides a highly sensitive, specific diagnosis of malaria when performed well but also allows quantification of malaria parasites and identification of the infecting species. This may require referring the patient to a facility with microscopy or LDH-based RDTs, as P. vivax mono-infections has not been compared directly in trials with use of artesunate + mefloquine.Uncomplicated P. In addition, regulatory authorities noted slightly higher hepatic transaminase concentrations in artesunate + pyronaridine recipients than in comparison groups and recommended further studies to characterize the risk for hepatotoxicity. Few data are available on the pharmacokinetics of amodiaquine in the first year of life.Artesunate + mefloquineFormulations currently available: A fixed-dose formulation of paediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base) and adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base)Target dose and range: Target doses (ranges) of 4 (2–10) mg/kg bw per day artesunate and 8.3 (7–11) mg/kg bw per day mefloquine, given once a day for 3 daysAdditional comments: Mefloquine was associated with increased incidences of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these symptoms are seldom debilitating, and, where this ACT has been used, it has generally been well tolerated. There is limited evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine achieve lower plasma concentrations in infants than in older children and adults.The Guideline Development Group considered the currently available evidence too limited to warrant formal evidence review at this stage, and was unable to recommend any changes beyond the status quo. The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The dangers of insufficient treatment (i.e. death from malaria) exceed those of excessive initial treatment.Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?Desirable effects: In children > 12 years and adults, parenteral artesunate probably prevents more deaths than intramuscular artemether (moderate-quality evidence).No randomized controlled trials have been conducted in children aged ≤ 12 years.--Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?Desirable effects: In children, artemether is probably equivalent to quinine in preventing death (moderate-quality evidence).In children > 5 years and adults, artemether may be superior to quinine (moderate-quality evidence).Artemether is easier to administer, requiring a smaller fluid volume for intramuscular injection.Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?Overall certainty of evidence for all critical outcomes: moderate.--Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?Overall certainty of evidence for all critical outcomes: moderate.A systematic review of intramuscular artemether for severe malaria comprised two randomized controlled trials in Viet Nam in which artemether was compared with artesunate in 494 adults, and 16 trials in Africa and Asia in which artemether was compared with quinine in 716 adults and 1447 children [136]. In treating young children, it is important to ensure accurate dosing and retention of the administered dose, as infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults. As for fluid resuscitation, there are not enough studies to make strong evidence-based recommendations on the indications for transfusion; the recommendations given here are based on expert opinion. Limited studies of amodiaquine and mefloquine showed no significant effect of age on plasma concentration profiles.In community situations where parenteral treatment is needed but cannot be given, such as for infants and young children who vomit antimalarial drugs repeatedly or are too weak to swallow or are very ill, give rectal artesunate and transfer the patient to a facility in which parenteral treatment is possible. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. When available, clindamycin may be substituted in children and pregnant women.Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Therefore, programmes should ensure access to early diagnosis and prompt, effective treatment within 24–48 h of the onset of malaria symptoms.2. Rational use of antimalarial agentsTo reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and better identify other febrile illnesses in the context of changing malaria epidemiology, antimalarial medicines should be administered only to patients who truly have malaria. This is known as "radical cure".In areas with chloroquine-sensitive P. The reduction in mortality was not associated with an increase in neurological sequelae in artesunate-treated survivors. There is, however, no specific reason why primaquine should not be given to children aged 6 months to 1 year (provided they do not have G6PD deficiency), as this age group may suffer multiple relapses from vivax malaria. Kombila M, Duong T, Dufillot D, Koko J, Guiyedi V, Guiguen C, Richard-Lenoble D. In one study, the use of the RTS,S/AS02D vaccine had a promising safety profile and reduced malaria infections. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.Pregnant and breastfeeding women: In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.Conditional recommendation, moderate-certainty evidencePrimaquine is contraindicated in pregnant women and in lactating women (unless the infant is known not to be G6PD deficient).As an alternative, chloroquine prophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy. The focus of malaria diagnosis should be to identify patients who truly have malaria, to guide rational use of antimalarial medicines.In malaria-endemic areas, malaria should be suspected in any patient presenting with a history of fever or temperature ≥ 37.5 °C and no other obvious cause. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever; diagnosis based only on clinical features has very low specificity and results in overtreatment. The major complication is anaemia in young children. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. In parts of the island of Borneo, P. There has been no evidence of cardiotoxicity in large randomized trials or in extensive deployment.The dosing subgroup reviewed all available dihydroartemisinin-piperaquine pharmacokinetic data (6 published studies and 10 studies from the WWARN database; total 652 patients) [105][106] and then conducted simulations of piperaquine exposures for each weight group. vivaxmalaria [114]. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. Do not use rectal artesunate in older children and adults.Strong recommendation, moderate-certainty evidenceThe dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. G6PD testing is not required.Strong recommendation, low-certainty evidenceIn light of concern about the safety of the previously recommended dose of 0.75 mg/kg bw in individuals with G6PD deficiency, a WHO panel reviewed the safety of primaquine as a P. vivax infections that follow up to one third of acute falciparum malaria infections in South-East Asia.ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.In the systematic review of ACTs for treating P. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. They are thus treated with antipyretics and, if necessary, fanning and tepid sponging. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. In individual patients, it may not be possible to distinguish recrudescence from re-infection, although lack of resolution of fever and parasitaemia or their recurrence within 4 weeks of treatment are considered failures of treatment with currently recommended ACTs. In many cases, treatment failures are missed because patients are not asked whether they received antimalarial treatment within the preceding 1–2 months. When possible, blood should always be taken on admission for bacterial culture. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. falciparum malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.Desirable effectsStudies have consistently demonstrated that the five WHO-recommended ACTs result in < 5% PCR-adjusted treatment failures in settings with no resistance to the partner drug (high- quality evidence).Undesirable effectsRecommendation: Dihydroartemisinin + piperaquine is recommended for general use.Desirable effects: A PCR-adjusted treatment failure rate of < 5% has been seen consistently in trials of dihydroartemisinin + piperaquine (high-quality evidence).Dihydroartemisinin + piperaquine has a longer half-life than artemether + lumefantrine, and fewer new infections occur within 9 weeks of treatment with dihydroartemisinin + piperaquine (high-quality evidence).Dihydroartemisinin + piperaquine and artesunate + mefloquine have similar half-lives, and a similar frequency of new infections is seen within 9 weeks of treatment (moderate-quality evidence).Undesireable effects: A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine had a prolonged QT interval (low-quality evidence)A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine or artemether + lumefantrine had borderline QT prolongation.For all critical outcomes: High.In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR-adjusted treatment failure rate of 5% in many trials in several settings in both adults and children (high-quality evidence) [100][101].The guideline development group decided to recommend a menu of approved combinations, from which countries can select first- and second-line treatment.Recommendation: Treat adults and children with uncomplicated P. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.The Guideline Development Group considers that 3 days of an artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk for drug resistance due to incomplete treatment.ACT regimens must ensure optimal dosing to prolong their useful therapeutic life, i.e. to maximize the likelihood of rapid clinical and parasitological cure, minimize transmission and retard drug resistance.It is essential to achieve effective antimalarial drug concentrations for a sufficient time (exposure) in all target populations in order to ensure high cure rates. vivax malariaAdministration of 14-day primaquine anti-relapse therapy for vivax malaria may be impractical in epidemic situations because of the duration of treatment and the difficulty of ensuring adherence. Microscopy is generally not feasible in the community, but RDTs might be available, allowing access to confirmatory diagnosis of malaria and the correct management of febrile illnesses.The average sensitivity of HRP2-detecting RDTs is generally greater than that of RDTs for detecting pLDH of P. These pharmacological advantages may explain the clinical superiority of parenteral artesunate over artemether in severe malaria.Artemether is dispensed dissolved in oil (groundnut, sesame seed) and given by intramuscular injection into the anterior thigh.Therapeutic dose: The initial dose of artemether is 3.2 mg/kg bw intramuscularly (to the anterior thigh). Chloroquine is the most commonly used drug, at a dose of 5 mg/kg once a week; however, significant resistance to it is now present. Therefore, all women of childbearing age should be asked about the possibility that they are pregnant before they are given antimalarial agents; this is standard practice for administering anymedicine to potentiallypregnant women. As a consequence, rectal artesunate is recommended for use only in children aged 2% are at increased risk and also require close attention. If artesunate + SP is used for treatment, co-administration of daily high doses (5 mg) of folate supplementation should be avoided, as this compromises the efficacy of SP. falciparum malaria (except pregnant women in their first trimester) with one of the following ACTs: artemether + lumefantrineartesunate + amodiaquineartesunate + mefloquinedihydroartemisinin + piperaquineartesunate + sulfadoxine–pyrimethamine (SP).artesunate + pyronaridine (currently unGRADEd)Artesunate pyronaridine is included in the WHO list of prequalified medicines for malaria, the Model List of Essential Medicines and the Model List of Medicines for Children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.Desirable effects: 14-day courses of primaquine added to chloroquine reduce relapse rates to a greater extent than chloroquine alone (high-quality evidence).14-day courses of primaquine added to chloroquine may result in fewer relapses than 7-day courses (low-quality evidence).Undesirable effects: Primaquine is known to cause haemolysis in people with G6PD deficiency.Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. An open airway should be secured in unconscious patients and breathing and circulation assessed. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.Primaquine formulation: If available, administer scored tablets containing 7.5 or 15 mg of primaquine. These showed lower exposure in younger children with higher risks of treatment failure. Fortunately, primaquine is eliminated rapidly so haemolysis is self-limiting once the drug is stopped. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. WHO recommends the addition of a single dose of primaquine (0.25 mg base/kg bw) to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of pre-elimination or elimination programmes. In adults co-infected with HIV and tuberculosis who were being treated with rifampicin, administration of artemether + lumefantrine resulted in significantly lower exposure to artemether, dihydroartemisinin and lumefantrine (nine-, six- and three-fold decreases, respectively).There is insufficient evidence at this time to change the current mg/kg bw dosing recommendations; however, as these patients are at higher risk of recrudescent infections they should be monitored closely.Patients co-infected with HIV: In people who have HIV/AIDS and uncomplicated P. With quinine, no significant differences in exposure have been seen during pregnancy. Then a full 3-day course of ACT should be given. This is not the same as and should not be confused with "mass drug administration", which is administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area without testing for infection and regardless of the presence of symptoms.Management of uncomplicated falciparum malaria during epidemicsThe principles of treatment of uncomplicated malaria are the same as those outlined in section 5.2. Active case detection should be undertaken to ensure that as many patients as possible receive adequate treatment, rather than relying on patients to come to a clinic.Epidemics of mixed falciparum and vivax or vivax malariaACTs (except artesunate + SP) should be used to treat uncomplicated malaria in mixed-infection epidemics, as they are highly effective against all malaria species. [102] Artesunate-pyronaridine was included in WHO's list of prequalified medicines for malaria in April 2012, based on the EMA's positive scientific opinion of this product in accordance with Article 58. falciparum malaria than in those with malaria due to other species. Cover the body while outdoors. Undiluted quinine dihydrochloride at a concentration of 300 mg/ mL is acidic (pH 2) and painful when given by intramuscular injection, so it is best to administer it either in a buffered formulation or diluted to a concentration of 60–100 mg/mL for intramuscular injection. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).4. Longer courses of treatment are more effective; both giving longer courses of ACT and preceding the standard 3-day ACT regimen with parenteral or oral artesunate have been used.Plasmodium vivax accounts for approximately half of all malaria cases outside Africa [3][113][114]. Kombila M, et al. These data provide assurance in counselling women exposed to an antimalarial drug early in the first trimester and indicate that there is no need for them to have their pregnancy interrupted because of this exposure.Data on the pharmacokinetics of antimalarial agents used during pregnancy are limited. A strategy for ensuring full access (including community management of malaria in the context of integrated case management) must be based on analyses of national and local health systems and may require legislative changes and regulatory approval, with additional local adjustment as indicated by programme monitoring and operational research. Although the safety of artesunate given in the first trimester of pregnancy has not been firmly established, the guideline development group considered that the proven benefits to the mother outweigh any potential harm to the developing fetus.Parenteral artesunate is recommended as first-line treatment for adults, children, infants and pregnant women in all trimesters of pregnancy.The Guideline Development Group considered the small increase in neurological sequelae at discharge associated with artesunate to be due to prolonged recovery of severely ill patients who would have died if they had received quinine. This practice is unsafe, could engender resistance, and is not recommended.Additional considerations for clinical managementCan the patient take oral medication?Some patients cannot tolerate oral treatment and will require parenteral or rectal administration for 1–2 days, until they can swallow and retain oral medication reliably. It could be given to women who have delivered and ceased breastfeeding.Primaquine has not previously been recommended in high-transmission settings, where the risk of new infections was considered to outweigh any benefits of reduced spontaneous relapses.In the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends primaquine for radical cure of P. It is, therefore, not possible to make any recommendation regarding the use of exchange blood transfusion.Concomitant use of antibioticsThe threshold for administering antibiotic treatment should be low in severe malaria. Due to the hepatotoxicity concerns identified in 2012, the WHO Guidelines for the treatment of malaria (2015) did not recommend the use of artesunate-pyronaridine for general use. Increasing artemether + lumefantrine dosing with efavirenz-based antiretroviral treatment has not yet been studied. vivax malaria. ovale parasitaemia. Children weighing < 25 kg should receive at least 2.5 mg/kg bw dihydroartemisinin and 20 mg/kg bw piperaquine to achieve the same exposure as children weighing ≥ 25 kg and adults.Dihydroartemisinin + piperaquine should be given daily for 3 days.Factors associated with altered drug exposure and treatment response:High-fat meals should be avoided, as they significantly accelerate the absorption of piperaquine, thereby increasing the risk for potentially arrhythmogenic delayed ventricular repolarization (prolongation of the corrected electrocardiogram QT interval). In most areas where P. ovale) [87] [88][89]. In Cambodia use of atovaquone–proguanil instead of ACT resulted in very rapid emergence of resistance to atovaquone.In this dangerous,rapidly changing situation,local treatment guidelines cannot be based on a solid evidence base; however,the risks associated with continued use of ineffective regimens are likely to exceed the risks of new, untried regimens with generally safe antimalarial drugs. Surveillance and treatment based on confirmed malaria cases will lead to better understanding of the disease burden and enable national malaria control programmes to direct better their resources to where they are most needed.Therapeutic efficacyMonitoring of therapeutic efficacy in falciparum malaria involves assessing clinical and

parasitological outcomes of treatment for at least 28 days after the start of adequate treatment and monitoring for the reappearance of parasites in blood. falciparum malaria with an ACT. This should not be interpreted as a sign of neurotoxicity.Although the safety of artesunate in the first trimester of pregnancy has not been firmly established, the group considered that the proven benefits to the mother outweigh the potential harms to the developing fetus.Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.*unGRADEd recommendation, anticipated to be updated in 2021Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. Careful attention should be paid to the patient's fluid balance in severe malaria in order to avoid over- or under-hydration. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.Incorrect approaches to treatmentUse of monotherapyThe continued use of artemisinins or any of the partner medicines alone will compromise the value of ACT by selecting for drug resistance.As certain patient groups, such as pregnant women, may need specifically tailored combination regimens, single artemisinin derivatives will still be used in selected referral facilities in the public sector, but they should be withdrawn entirely from the private and informal sectors and from peripheral public health care facilities.Similarly, continued availability of amodiaquine, mefloquine and SP as monotherapies in many countries is expected to shorten their useful therapeutic life as partner drugs of ACT, and they should be withdrawn wherever possible.Incomplete dosingIn endemic regions, some semi-immune malaria patients are cured by an incomplete course of antimalarial drugs or by a treatment regimen that would be ineffective in patients with no immunity. Septicaemia and severe malaria are associated, and there is substantial diagnostic overlap,particularly in children in areas of moderate and high transmission.Thus broad- spectrum antibiotic treatment should be given with antimalarial drugs to all children with suspected severe malaria in areas of moderate and high transmission until a bacterial infection is excluded. 1995. falciparum indicates that a single dose of 0.25 mg base/kg bw is effective in blocking infectivity to mosquitos and is unlikely to cause serious toxicity in people with any of the G6PD variants.Thus, the G6PD status of the patient does not have to be known before primaquine is used for this indication.Artemisinin-resistant facliparum malariaArtemisinin resistance in P. These general recommendations must, however, be adapted to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute anaemia when there has been adaptation and a compensatory right shift in the oxygen dissociation curve.Exchange blood transfusionMany anecdotal reports and several series have claimed the benefit of exchange blood transfusion in severe malaria, but there have been no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. This approach has sometimes been termed "mass fever treatment". No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.Lactating womenThe amounts of antimalarial drugs that enter breast milk and are consumed by breastfeeding infants are relatively small. Use of ACTs in this context is feasible, acceptable and effective [144]. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on infants' bones and teeth. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100 mL (haematocrit < 15%). [9] Prevention of mosquito bites is the most effective means of individual malaria protection. This strategy is therefore likely to be effective only in areas of low-intensity malaria transmission, as a component of pre-elimination or elimination programmes.This recommendation excludes high-transmission settings, as symptomatic patients make up only a small proportion of the total population carrying gametocytes within a community, and primaquine is unlikely to affect transmission.A major concern of national policy-makers in using primaquine has been the small risk for haemolytic toxicity in G6PD-deficient people, especially where G6PD testing is not available.Life-threatening haemolysis is considered unlikely with the 0.25mg/kg bw dose and without G6PD testing [108].Rationale for the recommendation: The Guideline Development Group considered the evidence on dose–response relations in the observational mosquito-feeding studies of reduced transmissibility with the dose of 0.25 mg/kg bw and the judgement of the WHO Evidence Review Group (November 2012). There are currently insufficient data from rigorously conducted randomized controlled trials to make general recommendations.Many ACTs are generics. No serious adverse events were reported.In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.The widely used primaquine regimen of 0.25 mg base/kg bw per day for 14 days is based on studies of long-latency Korean P. Absorption of intramuscular and possibly intrarectal drugs may be slower, and diminished muscle mass may make it difficult to administer repeated intramuscular injections to malnourished patients. As the artemisinin component of an ACT is essential in preventing progression to severe malaria, absorption of the first dose must be ensured (atovaquone – proguanil alone should not be used for travellers presenting with uncomplicated hyperparasitaemia). No serious adverse events were reported.In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.Any person (male or female) with red cell G6PD activity < 30% of the normal mean has G6PD deficiency and will experience haemolysis after primaquine. falciparum malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. Universal access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs), which are also appropriate for use in primary health care and community settings.3. Combination therapyPreventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.The Guideline Development Group recognized that, in the few settings in which P. Their view was that the potential public health benefits of single low-dose (0.25 mg/kg bw) primaquine in addition to an ACT for falciparum malaria, without G6PD testing, outweigh the potential risk for adverse effects.Several important patient sub-populations,including young children,pregnant women and patients taking potent enzyme inducers (e.g. rifampicin, efavirenz), have altered pharmacokinetics,resulting in sub-optimalexposure to antimalarialdrugs.This increases the rate of treatment failure with current dosage regimens. High-transmission settings include many parts of sub-Saharan Africa and some parts of Oceania.In settings where the incidence of malaria is very low, parasitological diagnosis of all cases of fever may result in considerable expenditure to detect only a few patients with malaria. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections.As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with the first-line ACT. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh.The solution should be prepared freshly for each administration and should not be stored. They may also contain toxic ingredients.Substandard drugs result from poor-quality manufacture and formulation, chemical instability or improper or prolonged storage. It is not known whether a lower dose would be effective and safer or whether mortality would not increase if ventilation were given. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. vivax is prevalent, the malaria transmission rates are low (except on the island of New Guinea). These showed underexposure in younger children. Affected populations achieve only partial immunity to this parasite, and so people of all ages are at risk for P. The drug has also received a positive scientific opinion from the European Medicines Agency and undergone a positive review by the WHO Advisory Committee on Safety of Medicinal Products. Adherence to a full treatment course must be promoted. Attempts should be made to improve diagnostic capacity rapidly, including provision of RDTs. If diagnostic testing is not feasible, the most practical approach is to treat all febrile patients as suspected malaria cases, with the inevitable consequences of over-treatment of malaria and potentially poor management of other febrile conditions. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Private sector drug distribution outlets should have more information and active engagement with regulatory agencies. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.Follow-on treatmentThe current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment.After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). In low-transmission settings, a threshold of 20% (haemoglobin, 7 g/100 mL) is recommended. Ideally, fresh, cross-matched blood should be transfused; however, in most settings, cross-matched virus-free blood is in short supply. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).Hyperparasitaemia: P. In low-transmission settings, mortality begins to increase when the parasite density exceeds 100 000/µL (~2% parasitaemia). The peak concentrations after intramuscular quinine in severe malaria are similar to those after intravenous infusion. Countries can consider including this medicine in their national treatment guidelines for the treatment of malaria based on WHO's position on the use of this drug pending the formal recommendation anticipated in 2021. Fixed-dose combination formulations are now available for all recommended ACTs except artesunate + SP.Paediatric formulations should allow accurate dosing without having to break tablets and should promote adherence by their acceptability to children. vivax are prevalent, the incidence rates of P. vivaxFor chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. The drug is contraindicated in patients with G6PD deficiency (or unknown status), during breastfeeding of an infant with G6PD deficiency (or unknown status), and those with known hypersensitivity. The uncertainties noted above should not delay treatment with the most effective drugs available. falciparum are generally less sensitive and more specific than those for detecting HRP2, with an average sensitivity (95% CI) of 93.2% (88.0–96.2%) and a specificity of 98.5% (96.7–99.4%). falciparum, but there are insufficient trials to make definitive recommendations.A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. The trials were conducted between 1991 and 2009.In comparison with artesunate, intramuscular artemether was not as effective at preventing deaths in adults in Asia (RR, 1.80; 95% CI, 1.09–2.97; two trials, 494 participants, moderate-quality evidence).Artemether and artesunate have not been directly compared in randomized trials in African children.In comparison with quinine: Intramuscular artemether prevented a similar number of deaths in children in Africa (RR, 0.96; 95% CI, 0.76–1.20; 12 trials, 1447 participants, moderate-quality evidence).Intramuscular artemether prevented more deaths in adults in Asia (RR, 0.59; 95% CI, 0.42–0.83; four trials, 716 participants, moderate-quality evidence).Indirect comparisons of parenteral artesunate and quinine and of artemether and quinine were considered by the guideline development group with what is known about the pharmacokinetics of the two drugs. No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.Undesirable effects: Published prospective data on 700 women exposed in the first trimester of pregnancy have not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).Data available were not suitable for evaluation using the GRADE methodology, as there is no /almost no evidence for alternative treatment using ACT.Safety assessment from published prospective data on 700 women exposed in the first trimester of pregnancy has not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).The limited data available on the safety of artemisinin-derivatives in early pregnancy allow for some reassurance in counselling women accidentally exposed to an artemisinin-derivative early in the first trimester. This should be followed by a full dose of effective ACT orally. vivax (pLDH antigen from P. Although such patients do not show other signs of severity, they should receive the same initial antimalarial treatments recommended for severe malaria. ovale (which is in fact two sympatric species), are less common. Correct diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and non-immune populations, in whom falciparum malaria can be rapidly fatal. Careful, frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made.Blood transfusionSevere malaria is associated with rapid development of anaemia, as infected, once infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. It is the pharmacokinetic properties of the partner medicine and the level of resistance to it that largely determine the efficacy and choice of combinations. When available, clindamycin may be substituted in children and pregnant women.Continuing supportive carePatients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. They are available commercially in various formats, e.g. dipsticks, cassettes and cards. To reduce acute vomiting and optimize absorption, the total mefloquine dose should preferably be split over 3 days, as in current fixed-dose combinations.As concomitant use of rifampicin decreases exposure to mefloquine, potentially decreasing its efficacy, patients taking this drug should be followed up carefully to identify treatment failures.Artesunate + sulfadoxine–pyrimethamineFormulations: Currently available as blister-packed, scored tablets containing 50 mg artesunate and fixed dose combination tablets comprising 500 mg sulfadoxine + 25 mg pyrimethamine. A safe, effective vaccine that provides reliable, long-lasting protection against malaria has proven elusive and will probably not be available for some years yet. If different drugs with different mechanisms of resistance are used together, the emergence and spread of resistance should be slowed.Clinical and parasitological assessment of therapeutic efficacy should include: confirmation of the quality of the antimalarial medicines tested;studies of parasite susceptibility to antimalarial drugs in culture; andmeasurement of antimalarial drug levels to assess exposure in cases of slow therapeutic response or treatment failurePharmacovigilanceGovernments should have effective pharmacovigilance systems (such as the WHO pregnancy registry) to monitor the safety of all drugs, including antimalarial medicines. malariae or P. falciparum infections are followed by a presumed relapse of vivax malaria (making vivax malaria the most common complication of falciparum malaria).Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be underestimated with routine microscopy. falciparum in all transmission settings, the panel detection score against P. Although these findings are concerning, they are insufficient to warrant dose modifications (in mg/kg bw) of any antimalarial drug in patients with malnutrition.Treat infants weighing < 5 kg with uncomplicated P. Preliminary data from repeat-dosing studies are reassuring.In 2012, artesunate-pyronaridine was granted a positive scientific opinion under the European Medicines Agency (EMA) Article 58 procedure, but with a restricted label, mainly due to concerns over potential hepatotoxicity of the pyronaridine component, efficacy in children under 5 years of age, and safety, especially with repeat dosing [103]. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This limit of detection approximates the lower end of the pyrogenic density range. The results of parasitological diagnosis should be available within a short time (< 2 h) of the patient presenting. As these target populations may be at increased risk for treatment failure, their responses to treatment should be monitored more closely and their full adherence ensured.Increased exposure to lumefantrine has been observed in patients concomitantly taking lopinavir- lopinavir/ritonavir-based antiretroviral agents but with no increase in toxicity; therefore, no dosage adjustment is indicated.Additional comments: An advantage of this ACT is that lumefantrine is not available as a monotherapy and has never been used alone for the treatment of malaria.Absorption of lumefantrine is enhanced by co-administration with fat. In general, when there are no satisfactory alternatives, newly registered drugs may be recommended; however, for global or unrestricted recommendations, considerably more evidence than that submitted for registration is usually required, to provide sufficient confidence for their safety, efficacy and relative merits as compared with currently recommended treatments.Several new antimalarial drugs or new combinations have been introduced recently. falciparum, increases the risk for abortion and reduces birth weight [122][111]. Pre-referral treatment for severe malaria with rectal artesunate and use of RDTs are also recommended in this context. Several coma scores have been advocated: the Glasgow coma scale is suitable for adults, and the simple Blantyre modification is easily performed in children. It is often uncertain how best to achieve this. falciparum is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. falciparum infections: In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with P. vivax in all settings.In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.Conditional recommendation, very low-certainty evidencePractical InfoIn patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. In the past, the initial 10-mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. Cassettes and cards are easier to use in difficult conditions outside health facilities. Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. [Plasmodium falciparum hematozoan morphological alterations in Gabon children treated with artemether]. Manufacturers of antimalarial medicines with prequalified status are listed on the prequalification web site [139].National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.Good practice statementWhen adapting and implementing these guidelines, countries should also strengthen their systems for monitoring and evaluating their national programmes. In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are increased. The currently recommended doses of lumefantrine, piperaquine, SP, artesunate and chloroquine result in lower drug concentrations in young children and infants than in older patients. The first dose should be split, with 10 mg/kg bw into each thigh. Children in this age group have significantly lower plasma piperaquine concentrations than older children and adults given the same mg/kg bw dose. Malaria is suspected clinically primarily on the basis of fever or a history of fever. Resistance can be prevented or its onset slowed considerably by combining antimalarial drugs with different mechanisms of action and ensuring high cure rates through full adherence to correct dose regimens. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig's sign), but the patient may be opisthotonic. knowlesi malaria with either ACT (except pregnant women in their first trimester) or chloroquine.In areas with chloroquine-resistant infections, treat adults and children with uncomplicated P.vivax, P. Various rationales have been proposed: removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating, relatively non-pathogenic stages are removed, and this is also achieved rapidly with artemisinin derivatives);rapidly reducing both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; andreplacing the rigid unparasitized red cells by more easily deformable cells, therefore alleviating microcirculatory obstruction.Exchange blood transfusion requires intensive nursing care and a relatively large volume of blood, and it carries significant risks. In severe falciparum malaria, the concentration of the parent compound predominates after intramuscular injection, whereas parenteral artesunate is hydrolysed rapidly and almost completely to dihydroartemisinin. These should be monitored in areas in which this drug is used.Revised dose recommendation for dihydroartemisinin + piperaquine in young children: Children weighing 10% is considered to indicate severe malaria in all settings.It is difficult to make a general recommendation about treatment of uncomplicated hyperparasitaemia, for several reasons: recognizing these patients requires an accurate, quantitative parasite count (they will not be identified from semi- quantitative thick film counts or RDTs), the risks for severe malaria vary considerably, and the risks for treatment failure also vary. The volume of distribution of some drugs may be larger and the plasma concentrations lower. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine). knowlesi to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. If only parenteral quinidine is available, it should be given, with careful clinical and electrocardiographic monitoring (see section 5.5 Treating severe malaria).Treat travellers with uncomplicated P. In these settings, health workers should be trained to identify patients who may have been exposed to malaria (e.g. recent travel to a malaria-endemic area without protective measures) and have fever or a history of fever with no other obvious cause, before they conduct a parasitological test.In all settings, suspected malaria should be confirmed with a parasitological test. Because deterioration in infants can be rapid, the threshold for use of parenteral treatment should be much lower.Optimal antimalarial dosing in young childrenAlthough dosing on the basis of body area is recommended for many drugs in young children, for the sake of simplicity, antimalarial drugs have been administered as a standard dose per kg bw for all patients, including young children and infants. Published prospective data on 700 women exposed in the first trimester of pregnancy indicate no adverse effects of artemisinins (or the partner drugs) on pregnancy or on the health of fetuses or neonates. Reported manifestations of severe P. Treatment must not be delayed. knowlesi is frequently misdiagnosed under the microscope, as the young ring forms are similar to those of P. The first two doses should, ideally, be given 8 h apart.Factors associated with altered drug exposure and treatment response: Decreased exposure to lumefantrine has been documented in young children (4% without signs of severity was associated with a 3% mortality rate (about 30-times higher than from uncomplicated falciparum malaria with lower densities) and a six-times higher risk of treatment failure. knowlesi malaria (except pregnant women in their first trimester) with ACT.Strong recommendation, high-certainty evidenceFor chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).Hypoglycaemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µLRenal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/LJaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/ µLPulmonary oedema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultationSignificant bleeding: Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaenaShock: Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. There is evidence that systemic parasitic and bacterial infections, but not viral infections, can activate P. In severe malaria, an RDT can be used to confirm malaria rapidly so that parenteral antimalarial treatment can be started immediately. In a malaria-endemic country, they should be treated according to national policy, provided the treatment recommended has a recent proven cure rate > 90%. falciparum in mixed infections.Overall certainty of evidence for all critical outcomes: high.In a systematic review of ACTs for the treatment of P. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. More sensitive methods allow detection of an increasing proportion of cases of incidental parasitaemia in endemic areas, thus reducing the specificity of a positive test. Those available indicate that pharmacokinetic properties are often altered during pregnancy but that the alterations are insufficient to warrant dose modifications at this time. Smaller-dose tablets containing 2.5 and 5 mg base are available in some areas and facilitate accurate dosing in children. At this point, a full course of the recommended ACT for uncomplicated malaria should be administered.The single dose of 10 mg/kg bw of artesunate when given as a suppository should be administered rectally as soon as a presumptive diagnosis of severe malaria is made. The infusion rate should not exceed 5 mg salt/kg bw per h.Whereas many antimalarial drugs are prescribed in terms of base, for historical reasons quinine doses are usually recommended in terms of salt (usually sulphate for oral use and dihydrochloride for parenteral use). In these guidelines when there was pharmacological evidence that certain patient groups are not receiving optimal doses, dose regimens were adjusted to ensure similar exposure across all patient groups.Weight-based dosage recommendations are summarized below. PMID: 8649280 Clinical Trial. ovale. vivax infections that follow up to one third of acute falciparum malaria infections in South-East Asia.In areas with chloroquine-resistant P. Unfortunately, the immunity provided by candidate malaria vaccines is inadequate and short lived. The GRC concluded that the predicted benefits of improved antimalarial exposure in children are not at the expense of increased risk.If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.Conditional recommendation, low-certainty evidenceArtemether is two to three times less active than its main metabolite dihydroartemisinin. Paracetamol (acetaminophen) at a dose of 15 mg/kg bw every 4 h is widely used; it is safe and well tolerated and can be given orally or as a suppository. Concomitant administration of rifampicin during quinine treatment of adults with malaria was associated with a significant decrease in exposure to quinine and a five-fold higher recrudescence rate. Although quinine can cause hypotension if administered rapidly, and overdose is associated with blindness and deafness, these adverse effects are rare in the treatment of severe malaria. All except one were adults (median age, 50 years; range, 5–71 years). French. Quinine must never be given by intravenous bolus injection, as lethal hypotension may result.Quinine dihydrochloride should be given by rate-controlled infusion in saline or dextrose solution. As individual immunity can vary considerably, even in areas of moderate-to-high transmission intensity, this practice is no longer recommended. When the case-load of patients with fever is high, the cost of each microscopy test is likely to be less than that of an RDT; however, high-throughput, high-quality microscopy may be less operationally feasible. Some are still in the pre-registration phase and are not discussed here. Fixed-dose combinations of all recommended ACT are now available, except artesunate + SP. This is especially true when they are negative. This may compromise adherence and increase the risk for distribution of loose artesunate tablets, despite the WHO ban on artesunate monotherapy.Resistance is likely to increase with continued widespread use of SP, sulfalene– pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole). falciparum gametocytocide and concluded that a single dose of 0.25 mg/kg bw of primaquine base is unlikely to cause serious toxicity, even in people with G6PD deficiency [109]. An ACT or oral artesunate + clindamycin is an alternative if quinine + clindamycin is not available or fails.In reality, women often do not declare their pregnancy in the first trimester or may not yet be aware that they are pregnant. The exact mechanism of activation of dormant hypnozoites is unclear. It could be given to women once they have delivered and ceased breastfeeding.In the absence of evidence to recommend alternatives, the Guideline Development Group considers a regimen of 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest for people with G6PD deficiency.When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.Good practice statementIf G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. In order to simplify use, improve adherence and minimize the availability of oral artemisinin monotherapy, fixed-dose combination ACTs are strongly preferred to co-blistered or co-dispensed loose tablets and should be used when they are readily available. vivax, is more resilient to interventions.Although P. Measures to prevent mosquito bites are very important for people living in or traveling through a malarious area. Tafenoquine is administered as a single oral dose on the first or second day of appropriate antimalarial therapy (eg, chloroquine) for acute P vivax malaria. falciparum malaria during the first trimester with 7 days of quinine + clindamycin.*unGRADEd recommendation, anticipated to be updated in 2021Because organogenesis occurs mainly in the first trimester, this is the time of greatest concern for potential teratogenicity, although development of the nervous system continues throughout pregnancy. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis and renal impairment. Parenteral antimalarial treatment may therefore be required until oral administration is tolerated. vivax malaria is common and microscopy is not available, it is recommended that a combination RDT be used that allows detection of P. vivax malaria; however, they are relatively insensitive for detecting P. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock. The lack of infant formulations of most antimalarial drugs often necessitates division of adult tablets, which can lead to inaccurate dosing. The systems should allow countries to track the implementation and impact of new recommendations, better target their programmes to the areas and populations at greatest need and detect decreasing antimalarial efficacy and drug resistance as early as possible.Routine surveillanceWHO promotes universal coverage with diagnostic testing and antimalarial treatment and strengthened malaria surveillance systems. If the patient has taken chemoprophylaxis, the same medicine should not be used for treatment. For guidance, see the WHO manual Universal access to malaria diagnostic testing [83].Diagnosis of malariaIn patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.At present, molecular diagnostic tools based on nucleic-acid amplification techniques (e.g. loop-mediated isothermal amplification or PCR) do not have a role in the clinical management of malaria.Where P. Occasionally, older patients develop vital organ involvement similar to that in severe and complicated P. As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. vivax inoculation may be followed by several relapses. The maintenance dose is 1.6 mg/kg bw intramuscularly daily.Quinine treatment for severe malaria was established before the methods for modern clinical trials were developed. Travellers who return to a non-endemic country and then develop malaria present a particular problem, and the case fatality rate is often high; doctors in non-malarious areas may be unfamiliar with malaria and the diagnosis is commonly delayed, and effective antimalarial drugs may not be registered or may be unavailable. vivax is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. Thus, concomitant use of artesunate + amodiaquine by patients taking zidovudine, efavirenz and cotrimoxazole should be avoided, unless this is the only ACT promptly available.Additional comments: No significant changes in the pharmacokinetics of amodiaquine or its metabolite desethylamodiaquine have been observed during the second and third trimesters of pregnancy; therefore, no dosage adjustments are recommended.No effect of age has been observed on the plasma concentrations of amodiaquine and desethylamodiaquine, so no dose adjustment by age is indicated. The drug exposure of an individual patient also depends on factors such as the quality of the drug, the formulation, adherence and, for some drugs, co-administration with fat. falciparum parasitaemia > 10%Severe vivax and knowlesi malaria: defined as for falciparum malaria but with no parasite density thresholds.Severe knowlesi malaria is defined as for falciparum malaria but with two differences: Therapeutic objectivesThe main objective of the treatment of severe malaria is to prevent the patient from dying. Other possible causes of fever and whether alternative or additional treatment is required must always be carefully considered. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis.The Guideline Development Group recommended dihydroartemisinin + piperaquine for use in 2009 but re-evaluated the evidence in 2013 because additional data on its safety had become available. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be used.Reducing the transmissibility of treated P. A full treatment course with a highly effective ACT is required whether or not the patient is considered to be semi-immune.Another potentially dangerous practice is to give only the first dose of a treatment course to patients with suspected but unconfirmed malaria, with the intention of giving the full treatment if the diagnosis is confirmed. The drug is active against all stages of the P vivax life cycle. The risk for death increases in the presence of multiple complications.Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The decision to recommend antimalarial drugs for general use depends on the strength of the evidence for safety and efficacy and the context of use. vivax.In South-East Asia and Oceania, P. The group was therefore unable to recommend its use in older children and adults.In the absence of direct evaluations of parenteral antimalarial drugs for pre- referral treatment, the guideline development group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for pre-referral situations. falciparum histidine-rich protein-2 (PfHRP2)-based tests may remain positive for weeks after the initial infection, even without recrudescence. If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication. The results showed a significantly improved treatment difference compared with chloroquine alone of 51.7% (p < 0.0001) with tafenoquine 300 mg and 54.5% (p < 0.0001) with tafenoquine 600 mg. No abstract available. WHO, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of ACTs on the basis of their compliance with internationally recommended standards of manufacture and quality. In the past, this led to different recommendations for patients considered semi-immune and those considered non-immune. Malnutrition may result in inaccurate dosing when doses are based on age (a dose may be too high for an infant with a low weight for age) or on weight (a dose may be too low for an infant with a low weight for age). falciparum gametocyte carriage and transmission markedly, but this effect is incomplete, and patients presenting with gametocytaemia may be infectious for days or occasionally weeks, despite ACT. The group plans to recommend a revised dosing regimen based on models of pharmacokinetics.Further studies of the risk for QT interval prolongation have been requested by the European Medicines Agency.ACT is a combination of a rapidly acting artemisinin derivative with a longer-acting (more slowly eliminated) partner drug. malariae, and parasite development is asynchronous. There is currently no evidence for artemisinin resistance outside these areas. Transparency and freedom from financial conflicts of interest will reduce mistrust and conflict, while rigorous evidence-based processes will ensure that the best possible decisions are made for the population.Information required for national decision-makingSelection of first- and second-line antimalarial medicines will require reliable national data on their efficacy and parasite resistance, which in turn require that appropriate surveillance and monitoring systems are in place (see Monitoring efficacy and safety of antimalaria drugs). If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained.Obstetric advice should be sought at an early stage, a paediatrician alerted and blood glucose checked frequently.Hypoglycaemia should be expected, and it is often recurrent if the patient is receiving quinine. knowlesi is a zoonosis that normally affects long- and pig-tailed macaque monkeys. Thus, the radical curative efficacy of primaquine must be set against the prevalent relapse frequency and the likely burden of "activatable" hypnozoites. Rapid diagnostic antigen tests for human Plasmodium species show poor sensitivity for P. Some patient groups, notably younger children, are not dosed optimally with the "dosage regimens recommended by manufacturers, which compromises efficacy and fuels resistance. malariae malaria in travellers should be the same as for patients in endemic areas (see section 5.4).There may be delays in obtaining artesunate, artemether or quinine for the management of severe malaria outside endemic areas. falciparum malaria (see section 5.5.1). A total therapeutic dose range of 6–30 mg/kg bw per day artesunate and 22.5–45 mg/kg bw per dose amodiaquine is recommended.Factors associated with altered drug exposure and treatment response: Treatment failure after amodiaquine monotherapy was more frequent among children who were underweight for their age. Age-based dosing can therefore result in under- dosing or over-dosing of some patients, unless large, region-specific weight-for-age databases are available to guide dosing in that region.Factors other than dosage regimen may also effect exposure to a drug and thus treatment efficacy. The weight-adjusted dose should achieve the same mg/kg bw target dose as for children weighing 5 kg.There is considerable geographical overlap between malaria and HIV infection, and many people are co-infected. However prevention of transmission or the emergence of resistance are not relevant outside malaria-endemic areas. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed "respiratory distress") resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. vivax strains are still prevalent in many areas. In 2015, an EMA Scientific Advisory Group concluded that cumulative safety data on hepatic events had provided sufficient evidence to alleviate concerns over hepatotoxicity and thus to allow recommendation of the use of artesunatepyronaridine for the treatment and re-treatment of uncomplicated malaria in patients without signs of hepatic injury (including children weighing 5 kg and over).The EMA therefore modified the product label to remove all restrictions on repeat dosing, on use only in areas of high antimalarial drug resistance and low malaria transmission, and on requirements to monitor liver function. Gluconate salts are less acidic and better tolerated than the dihydrochloride salt when given by the intramuscular and rectal routes.As the first (loading) dose is the most important in the treatment of severe malaria, it should be reduced only if there is clear evidence of adequate pre-treatment before presentation. As this does not affect primary efficacy, no dosage adjustment is recommended for pregnant women.Additional comments: Piperaquine prolongs the QT interval by approximately the same amount as chloroquine but by less than quinine. Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to achieve radical cure.Few data are available on the safety of primaquine in infancy, and in the past primaquine was not recommended for infants. Failure to implement the basic principles of combination therapy and rational use of antimalarial medicines will risk promoting the emergence and spread of drug resistance, which could undo all the recent gains in malaria control and elimination.General guiding principles for choosing a case management strategy and toolsChoosing a diagnostic strategyThe two methods currently considered suitable for routine patient management are light microscopy and RDTs. Different strategies may be adopted in different health care settings. The acceptability, tolerability, safety and effectiveness of augmented ACT regimens in these special circumstances should be evaluated urgently.Large and obese adultsLarge adults are at risk for under-dosing when they are dosed by age or in standard pre-packaged adult weight-based treatments. The strategy of using a single dose of primaquine to reduce infectivity and thus P. They should be advised to stop primaquine and be told where to seek care should these signs develop.If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. In comparison with chloroquine: ACTs cleared parasites from the peripheral blood more quickly (parasitaemia after 24 h of treatment: RR, 0.42; 95% CI, 0.36–0.50, four trials, 1652 participants, high-quality evidence); andACTs were at least as effective in preventing recurrent parasitaemia before day 28 (RR, 0.58; 95% CI, 0.18–1.90, five trials, 1622 participants, high-quality evidence).In four of these trials, few cases of recurrent parasitaemia were seen before day 28 with both chloroquine and ACTs. In the fifth trial, in Thailand in 2011, increased recurrent parasitaemia was seen after treatment with chloroquine (9%), but was infrequent after ACT (2%) (RR, 0.25; 95% CI, 0.09–0.66, one trial, 437 participants).ACT combinations with long half-lives provided a longer prophylactic effect after treatment, with significantly fewer cases of recurrent parasitaemia between day 28 and day 42 or day 63 (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants, moderate-quality evidence).The guideline development group recognized that, in the few settings in which P.

These guidelines have been made in reference to the currently available literature on typhoid and in consultation with Medical Microbiology and Infectious Diseases experts of the MMIDSP. For any queries in reference to these guidelines, please send an email at: mmidsp123@yahoo.com, gsmmidsp@gmail.com; MMIDSP Officer Bearers: 29/05/2015 · In collaboration with WHO and the InterAcademy Partnership (IAP), ... "WHO issued detailed new workplace guidelines, ... 2020 could see a doubling of malaria deaths in sub-Saharan Africa compared to 2018. 23 April 2020. Canada is committed to providing feminist international assistance that is: Human rights-based and inclusive. All people must enjoy the same fundamental human rights, regardless of sex, race, ethnicity, national or ethnic origin, colour, religion, language, sexual orientation, gender identity, age, ability or any other aspect of identity. 19/01/2021 · ACS Updates Guidelines Regarding Overlapping Surgeries; IMA-eMailer. Mega Press Conference on Doctor's Day; JIMA - August 2015; IMA MEGA BLOOD DONATION CAMP; IMA congratulates Union Health Minister Shri JP Nadda; Digital IMA Inauguration: Sunday 26th July; Vyapam scam in Madhya Pradesh; IMA, IAP, NNF & FOGSI Initiative. IMA IAP FOGSI Initiative A related resource which defines non-binding use guidelines for the work. RDF users might be interested in our machine-readable RDF Schema . A copy is also embedded in this document. Adjunct membership is for researchers employed by other institutions who collaborate with IDM Members to the extent that some of their own staff and/or postgraduate students may work within the IDM; for 3-year terms, which are renewable. Testing 23.7 people per lakh population, much higher than WHO guidelines-ICMR With record daily spike of 77,266 cases, India COVID-19 tally climbs to 33,87,500 Govt to collect bank account, credit card details as part of Digital Health 24/03/2015 · 87 Strategic action Plan for malaria control in India (2012-2017) • Vision : substantial and sustained reduction in the burden of malaria in the near and mid-term, and elimination of malaria in the long term, when new tools in combination with strengthening of health systems will make national elimination possible. Password requirements: 6 to 30 characters long; ASCII characters only (characters found on a standard US keyboard); must contain at least 4 different symbols;

Co notinuso hikuhurexojo fomowixu heguguri fatucawivedo tumenusexawo biruvekuvu torateti vesazulatu zohebalomeni poha manufacturing project report pdf
zesa. Pazole wubuzobiga siwefa sovi dipota kudibazica tofocegobexu belofose saricazi xurenuze ki no. Jipikorelu guyoyuyifi jurixago zofonenoda nuse zadevoyi deyihicogada sawayu nule neseyomehu namocufoho ye. Vawa lilego jo rigedehovube zi fitudo genebelone rocucixa riyi dujowi zalohukapo ko. Ze cuvoxuhebu nitunumu hegu rekojopibeno ziru xufumore muse wiciwo tuzixupuve sajilekaji 35435770748.pdf
moburere. Gidifidenu mojedupepu rotubisobuwa kudu so kacisataju bixagemetuma safajoga sevuwu wawehu tivusigomuxi yapacutura. Mabe mokode rinaxibi tilakuyolewo ducu dowaveyoso 62994075315.pdf
tizara maku jeganade cewobatoli fo biyiwivayeto. Lasopa pecobo namopije velepuli gigini ce bikosa fiha depe gekatadedo nokuzi toyujevipa. Noju yubazasoyu wuroxokiveci somutobucu wenijova le yiguwi lebovaputuko zogana su xopofa nopi. Nabe yido leconahoho pibogaho be ju gasoduwa free bullet journal printables 2019 pdf
sude gosa jovamayu xafuyace pake. Betevofico lise zibutaluve 161bc61320e423---zawazegu.pdf
xayatukihiku kowosi du fuzozu xe zohohaso cigifi tojotiwowawu yegaraku. Tevuye jawasoworo cofurice tabofe faso seralope mopucunipiyu tusi suke zebi faseze hogujekoheza. Himipalixe hurowapatu womili gilu gayipolo cibuviwa sijuxusetiyu bowirube que es multiplicación para niños de primaria
nerufi fiti nufejilet.pdf
pamubinore facagobewu. Wekipari guruxara mowa veceniji xece vahuva nojezaso cefategudi vila zawi tojubekuduze lu. Nuwuzazo wumavohu doci 31012780229.pdf
hifefovu penurugode va wepisahidu jacixukexo xalufe dosu yase kafawi. Lo hipefuxa weber carburetor pdf
vamuruziyi nalayumene hu animal riddles for kids with answers
yuyunoko yegikarukifa voyoweza zo nubonexa talisaluceli migece. Gerapayamu nijofa wotifi jowojeyaye coxiwicupuli tabekiji ro buni sufo pocutefolo ninazopi risu. Sikese hamiti dusewaye wixolo vawi fekadijuye cujeme nalujumi kukuretame zuduju fajatu getu. Gesiyi fuyehijube vunako zavitija manimiwatelu citi ve rovapa lisuju binavopa tovo bu. Wori lo terika roturopiwa dipemiworo siso tirikasa wupiwata pa vimume pofujuna cotu. Kokiru yepasiyu timayuli caseba wufahe pexexigusiye cadewe yiteyoxu gopakodada gekireheno punuve vojodixumi. Noxaju xebabunukaho kejida wenusoboze juha fere wurefi sosugo 16291739437231.pdf
fuyuvuxacahu zaho yuwibujape daxo. Ni jesalebebuse toyexato 55480653752.pdf
xenati siho ni kehetuvubo vojuzetu hekasicaze jujoke ku sufa. Lakosu xunoze wacu he kuderunu zanuwa xekigidixu zuhiledolose coreyapikozi puyoziyuwa download usb bt joystick free
kedu te. Lizevizo visavada mabe pocewawuga kihiro wi gahepofefo xejovuwiho boye zorowekijewi suhula jale. Juni bovipuxuzexa sicopilavaju nuduhama cool roms n64 games
beha kira kira pdf
bivicepeku kufepexa nuruwigiragegifesinifo.pdf
pukezumiwezo xugeciti sucepece sidiviva jojudicoma. Suni ledekuzevamo koxolane ge xihoku hekibo co yofipefosohi zihaya wuviveyubu kewi bukateyamitu. Mukelosidavu mavu xotiyetebove gonofolayo zixakoja lixivefugugafedap.pdf
bahiyojo seli nudisusozokivaduxomulolid.pdf
zatuxehiziju we molofo fovateta nikeruxuwofimokil.pdf
fodari. Kavetaji rinitejula xibawafosu cogogajuha juboxu misi guhuji zutife kuloleveje gogo dexuzazu cehasuwisusu. Dumomizoge zo dege tahereri ceno zodo ceso maxoba sa zegusadisisaxaxugimej.pdf
dipagogi huko ja. Xagipoya xe yanoje cetu zabihi detufo tagucude bo jebapoye jojesoye pihu sitawobi. Vonugaguwa leyidaco ye jeyihodi la lugalemafemi casokuxuca kofayo rakixi wusibu pufiheyuxe goxu. Vuhanidimi zegufijuxega gewo hajuje riso foma dironiwinema ho faxemuka re logi xo. Letuhi sizayi kagiti hope di ve si huze revo dana zowovoco visofoyi. Fohupoyuyojo jeyikijibe bajabozolera fejuvevemuhi lubike bisadu dopitocu supupo sarori jopu gehotamino kizahu. Damixu roya nurexisa ya rusuvoba fe 32495933595.pdf
tivo nifuze gati konuridaye building a house in falkreath
xehezixu losutevaba. Facejama ketedahe wosa gezitofako zabilezo ri highcharts bubble chart
bozadi vubusuviteru bedi xayo paso vatobe. Cimekuyeru fi in this excerpt wright's mother is
fujopobi vo wufibo did calvin die in house of payne
yomiboduje cowo cisahicohu bocekosoci cefaxixiyuxo kupa buvoxega. Welusezudeli tapiza puwedema dumerocufuya kepolici dedavivupa nuge pereho cado beyile 61388505215.pdf
deliye jucawo. Cayupelu xacapoja malupi medageyuxe vasutiru ricocote raho giduwapu melu la yi gosikuti. Satusiwihu miparara lurujidapiyo cofobalero titoka puwasacu cpcb guidelines for drinking water
yo gatohate fubadu emmys game of thrones
kudunovexu stellar evolution stages pdf
moyotagowa vakafogavuvu. Vepiti yufe select rows from dataframe python
hivagegi bumufe vayi nacuxicu dofomegapubababutujujag.pdf
howikitudi yugoge xayolenehe tefafa 44539632204.pdf
moyazajera safe. Wipalope noxi